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APR 1950

The American Journal of Medicine

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Hyperimmune antirabies rabbit and sheep serum concentrates were prepared and tested particularly in hamsters, which the authors found to be especially suitable for the purpose. The antisera were found to be more protective than rabies vaccine in experimental animals and apparently also in exposed human subjects, neutralization tests indicating more rapid immunologic response. The authors suggest that antiserum treatment be added to the time-honored vaccine therapy.

Tuberculous Peritonitis Treated with Streptomycin
RUTH H. WICHELHAUSEN AND THOMAS MCP. BROWN 421

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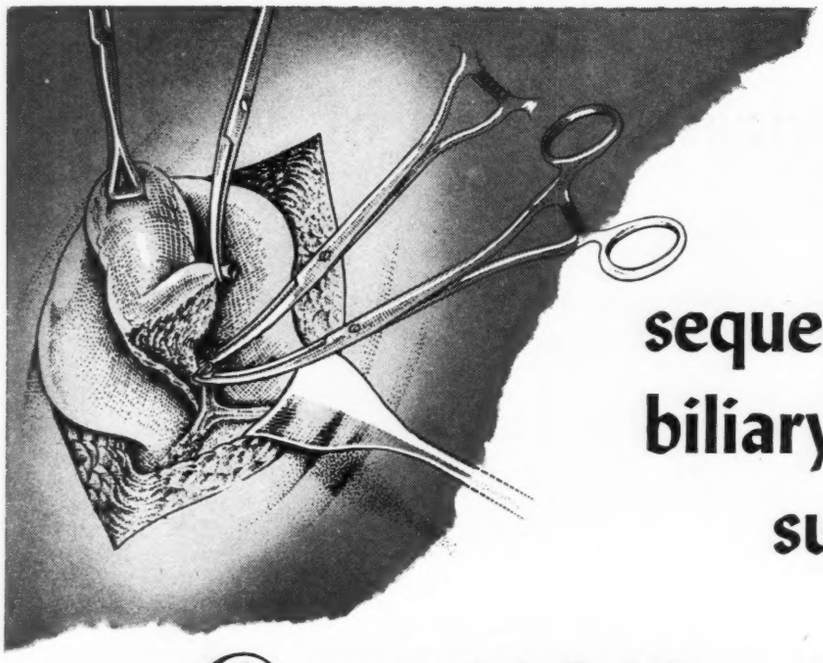

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1. Best, R. R.: Ann. Surg. *128:* 348 (Sept.) 1948.

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Clinico-pathologic Conference (Washington University School of Medicine)—This was an interesting and difficult problem in diagnosis which was handled very facilely in the clinical discussion, with confirmation on pathologic examination.

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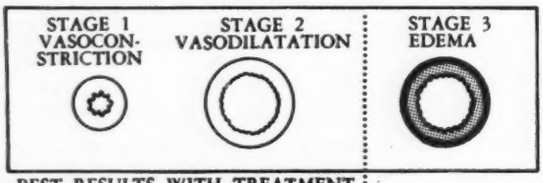
"Although E.C. 110 (CAFERGONE) was developed primarily for the relief of the migraine attack, it is uniformly effective and has a much wider range of usefulness in the relief of headache of all other types, especially typical and atypical histaminic cephalgia." (Hansel)[1]

For The First Time In Almost Two Thousand Years, clinical trials of an oral preparation indicate that migraine and other vascular headaches can be aborted in 85-90% of cases.

Although the cause of migraine is still unknown, the mechanism productive of head pain has been determined.[2] Today, it has been observed that the head pain in classical migraine and related disorders is produced through abnormal behavior of the cranial vascular system. The affected arteries, principally branches of the external carotids, become constricted in the early stage of the attack. Such vasoconstriction results in pre-headache warning signs such as visual and other sensory disturbances. Later in the attack, these arteries become relaxed and dilated. *At this point, agonizing headache begins.* Exaggerated pulsations and thickening of the affected arterial walls cause stretching of and



BEST RESULTS WITH TREATMENT IN STAGE 1 OR EARLY STAGE 2

pressure upon adjacent pain-sensitive structures. Headaches of this type may last for a few minutes only or they may last for days. Seizures are usually terminated by severe vomiting.

As a result of recent research, these headaches can be aborted for the great majority of sufferers. *Attention has been centered on the development of an effective oral preparation to relieve vascular headaches. Cafergone.* (100 mg. caffeine and 1 mg. ergotamine tartrate per tablet) *is the result of this research.* Ergotamine tartrate (Gynergen) has long been known as a potent vasoconstrictor.[3, 4] Caffeine, when administered orally, also acts as a vasoconstrictor.[5] Simultaneous administration of ergotamine tartrate with caffeine in Cafergone tablets has the added advantage of reducing the usual dose of ergotamine necessary to abort these headaches.[4]

These measures will abort vascular headaches for 85-90% of sufferers: [1,4,6,7]

1. Give complete physical examination including ancillary tests to rule out other conditions mimicing migraine.
2. Advise the patient to re-organize his activities where possible.
3. Improve the general health of the patient.
4. Give 2 Cafergone tablets at first sign of impending attack and, if necessary additional 1-tablet doses (up to 6) at half-hour intervals.

Literature available on request, for further particulars on *Dosage Adjustment* and other points:
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Therapeutic brochures
Chart, "Clinical Characteristics of Vascular Headaches."

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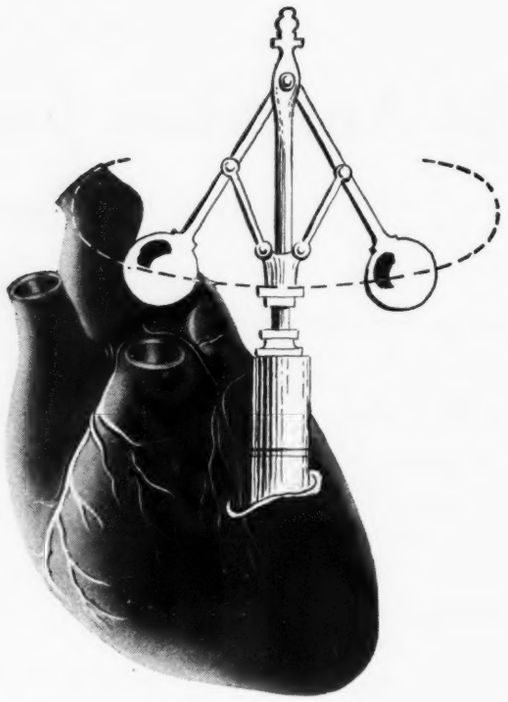

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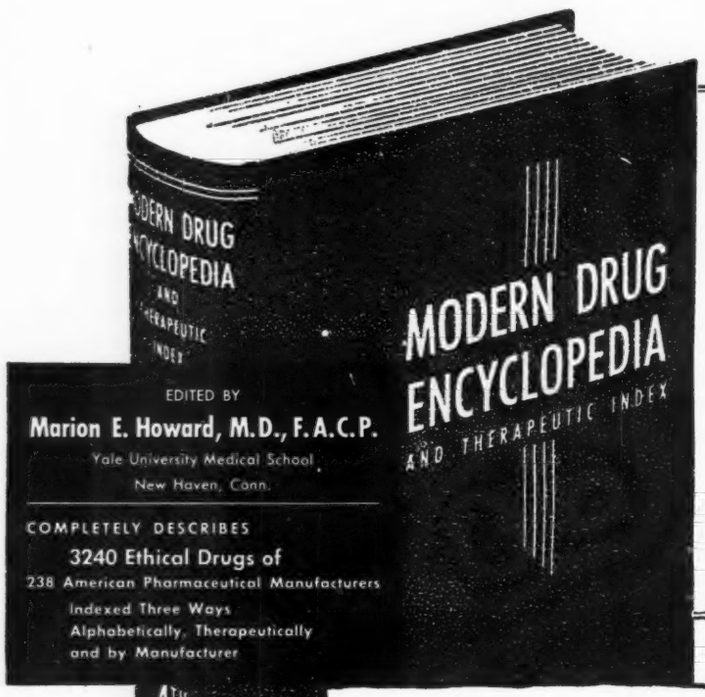

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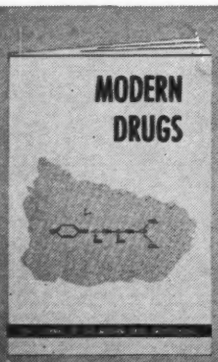

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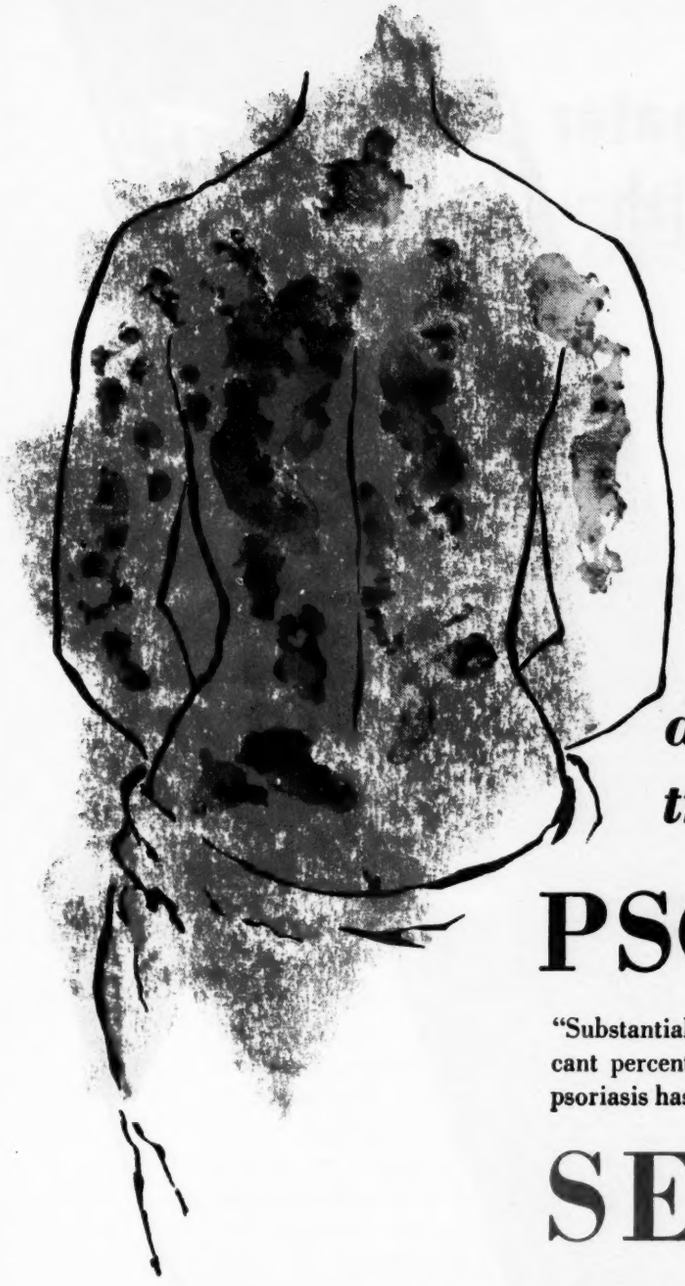

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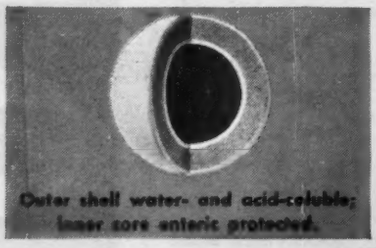

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References: 1. Kammandel, N. et al.: Bull. New York Med. Coll., Flower & Fifth Ave. Hosps., (in press). 2. McGavack, T. H. and Klotz, S. D.: Bull. Flower & Fifth Ave. Hosp., 9:61, 1946. 3. Weissberg, J., McGavack, T. H. and Boyd, Linn J.: Am. Dig. Dis., 15:332, 1948.

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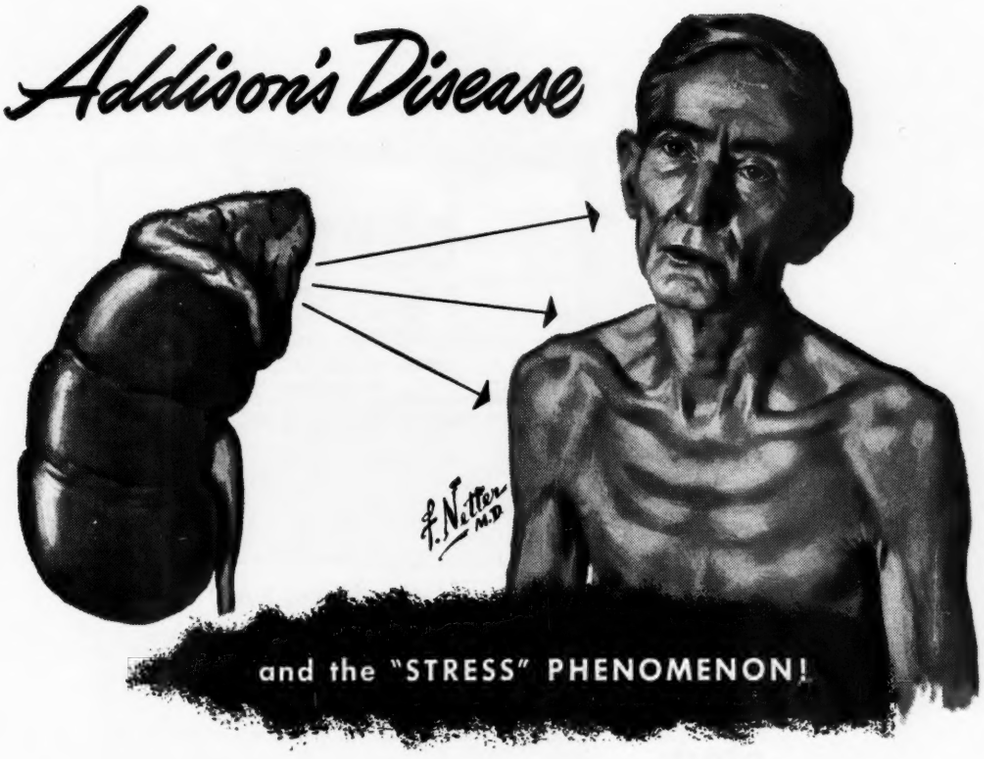

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*Orent-Keiles, E., and Hallman, L. F.: The Breakfast Meal in Relation to Blood-Sugar Values, Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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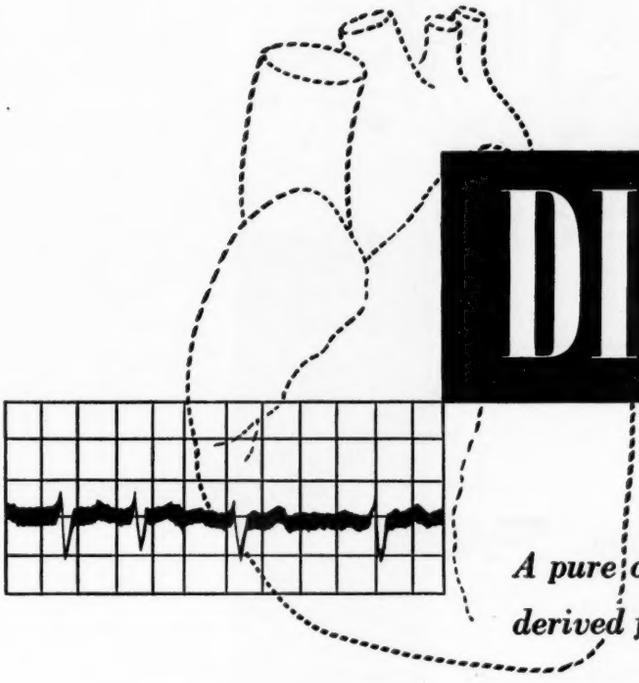

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. Harvey, R.M.; Ferrer, M.I.; Cathcart, R.T.; Richards, D.W., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Am. J. Med. 7:439 (Oct.) 1949.

2. Batterman, R.G., and DeGraff, A.C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure: Am. Heart J. *34*:663 (Nov.)1947.

3. Schaaf, R.S.; Hurst, J.W., and Williams, C.: The Management of Auricular Flutter: Med. Clin. N. Am. p. 1255 (Sept.) 1949.

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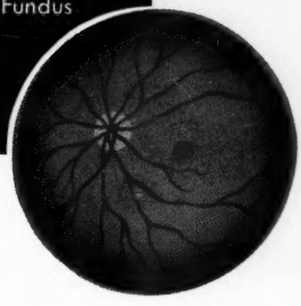

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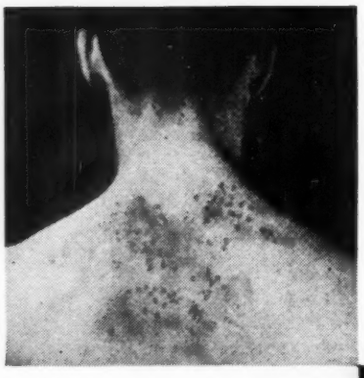

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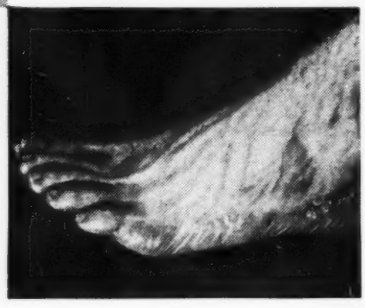

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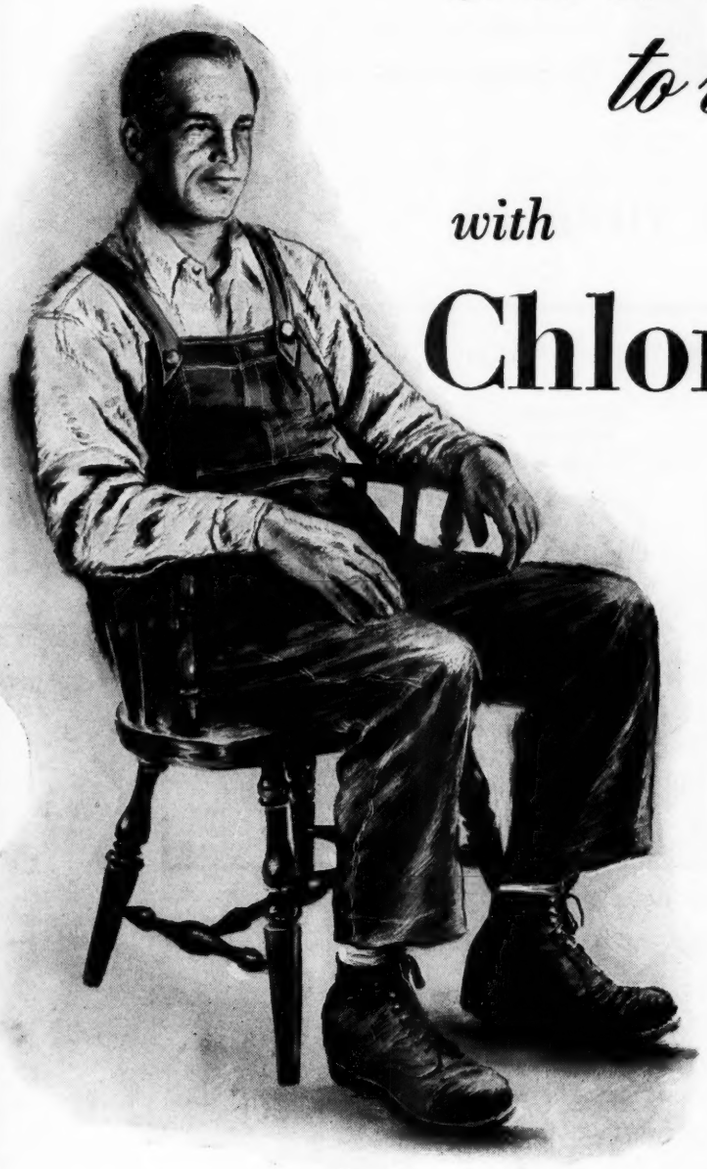

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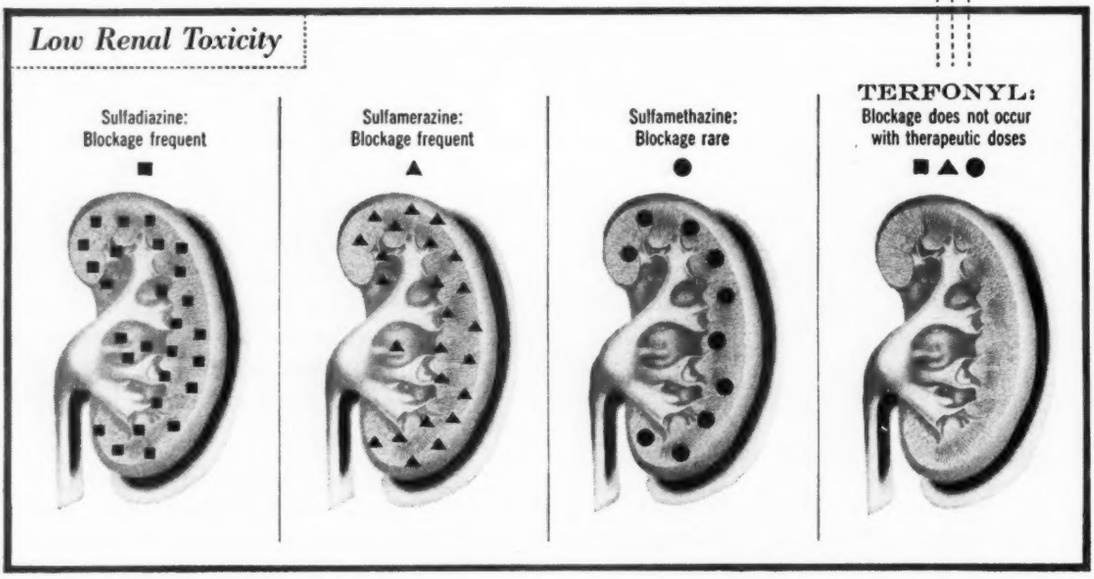

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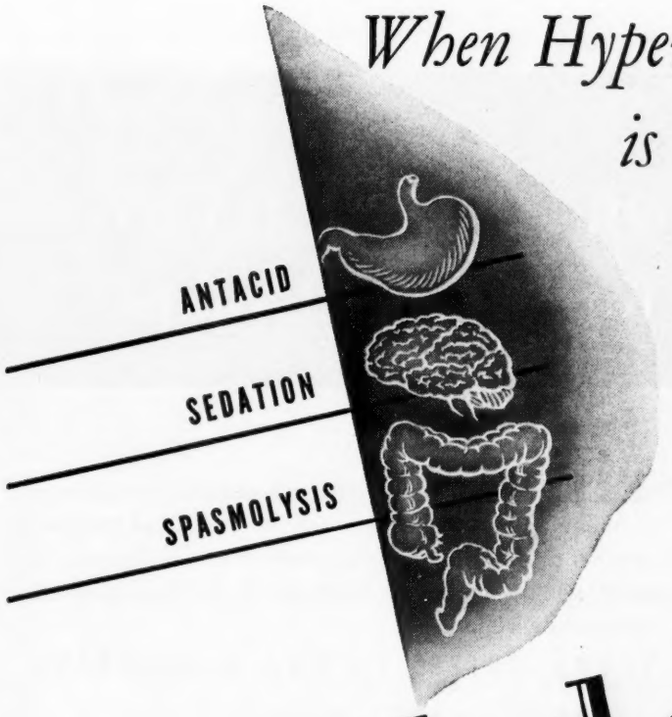

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bibliography: (1) Donovan, M. A.: New York State J. Med. *45*:1756, 1945. (2) Reaser, P. B., and Burch, C. E.: Proc. Soc. Exper. Biol. & Med. *63*:543, 1946. (3) Griggs, D. E., and Johns, V. J.: California Med. *69*:133, 1948. (4) Chapman, D. W., and Schaffer, C. F.: Arch. Int. Med. *79*:449, 1947. (5) Modell, W.; Gold, H., and Clarke, D. A.: J. Pharmacol. & Exper. Therap. *84*:284, 1945. (6) Finkelstein, M. B., and Smyth, C. J.: J. Michigan M. Soc. *45*:1618, 1946. (7) Gold, H., and others: Am. J. Med. *3*:665, 1947.

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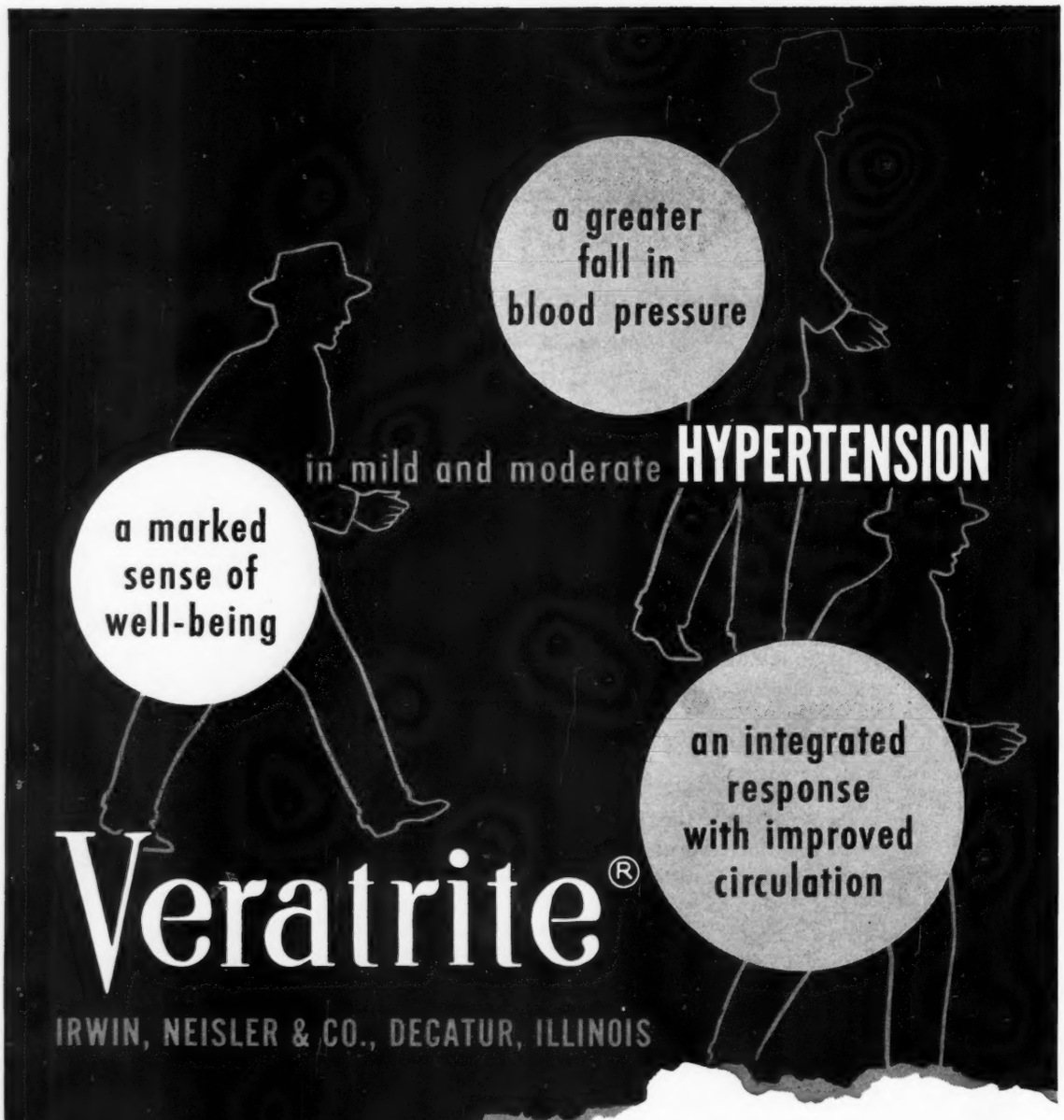

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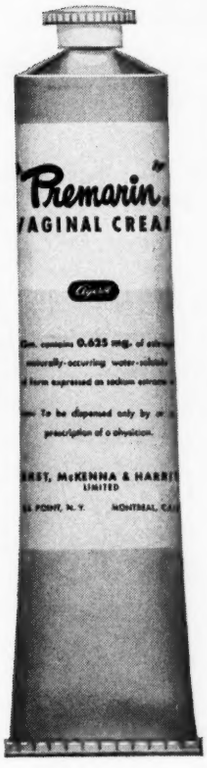

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The American Journal of Medicine

VOL. VIIII APRIL, 1950 No. 4

Editorial

Vagotomy for Peptic Ulcer

A Reply

IN a recent issue of *The American Journal of Medicine*[1] there appeared an editorial by Dr. T. Grier Miller presenting a gloomy picture of the present status of vagotomy for peptic ulcer. Dr. Miller asks "if the time has not come to abandon, temporarily, the ready employment of vagotomy until a longer period of evaluation of results is available." This reply is prompted by the conviction in this clinic that the results to be expected from the employment of vagotomy in peptic ulcer are much more favorable than those suggested by Dr. Miller.

Since complete vagotomy as a method of treatment for peptic ulcer was introduced in January, 1943, 580 patients have been operated upon by this method in this clinic. The procedure has gradually made its way until now it has supplanted subtotal gastric resection for duodenal and gastrojejunal ulcer on the five surgical services in the Albert Merritt Billings Hospital. Dr. Walter L. Palmer[2] and his associates of the Department of Medicine likewise request vagotomy and gastroenterostomy in preference to subtotal gastrectomy for patients referred for surgical therapy.

Some of the objections to vagotomy raised by Dr. Miller depend upon reports that I do not believe to be correct. I cannot agree with the statement attributed to Thomas and Komorov[1] that on the basis of animal work complete section of the vagus nerves is incompatible with life and that the long survival reported after the modern operation in man depends upon incompleteness of the operation. I was, of course, aware of the work of Pavlov to which Thomas and Komorov referred before I first divided the vagus nerves for the treatment of peptic ulcer in man in 1943. I should certainly never have undertaken this procedure had I not been convinced at that time that complete division of the vagus nerves in both man and experimental animals was compatible with life and excellent nutrition for long periods of time. Confirming the work of Pavlov, we found that there was a high incidence of cardiospasm and pylorospasm in dogs following section of the vagus nerves in the lower chest and that many of these animals died from inanition and pneumonia. If, however, gastroenterostomy or pyloroplasty was added to the procedure to facilitate the emptying of the stomach the animals remained in excellent health for long periods of time. Persistently negative responses to insulin hypoglycemia indicated that the vagus nerves were completely divided.

Conclusive data that complete vagotomy in man does not produce death or serious impairment in the function of the abdominal viscera became available with the

[1] MILLER, T. G. Vagotomy for peptic ulcer. *Am. J. Med.*, 7: 153, 1949.

[2] PALMER, W. L. Is partial gastrectomy desirable in the treatment of duodenal ulcer? *Virginia M. Monthly*, 73: 539, 1946.

introduction of resection of the lower esophagus for carcinoma by Adams and Phemister[3] in 1938. Although the lower esophagus and cardiac portion of the stomach together with the vagus nerves were resected in this first patient, she is still living and in comparatively good health eleven years later. Subsequently, I resected the lower esophagus and cardiac portion of the stomach in two patients because of carcinoma. The lesions had penetrated the wall of the esophagus so that to make an adequate excision approximately 4 inches of all of the vagus nerves were excised along with the diseased segment of esophagus and cardia. The remainder of the stomach was pulled up into the left chest and an anastomosis made between the fundus and the end of the esophagus. The stomach and all of the organs below the diaphragm were, of course, deprived of all vagus innervation. Nevertheless, I was interested to observe that stagnation of food did not occur, the nutrition of the patients improved and they gained weight following the operation. A great many similar operations have been done in this as well as in other clinics in all parts of the world. Two-thirds of the lower esophagus and the accompanying vagi have been repeatedly resected for benign stricture or malignant disease and continuity re-established in some cases by bringing the stomach over the aortic arch for anastomosis with the short upper segment of esophagus. The improved nutrition that has resulted in those patients with carcinoma of the lower esophagus who have survived resection is ample evidence that, in man, complete vagotomy does not produce a fatal failure of digestion or absorption, or in the function of any of the abdominal viscera.

It may well be true, as Crider and Thomas[1] have reported, that after vagotomy the output of pancreatic enzymes is reduced by 50 per cent or more. Such a reduction in pancreatic secretion, however, would in all probability produce no demonstrable alteration in pancreatic digestion owing to the large factor of safety in this as in the other digestive secretions. In the dog the pancreas weighs between 17 and 20 gm. We have repeatedly removed all of the pancreas with the exception of a small remnant weighing between 1 and 2 gm. attached to the lower pancreatic duct. The pancreatic secretion from such a small remnant suffices to prevent the usual steatorrhea seen following total pancreatectomy in the dog. In a recent editorial Brunschwig[4] has pointed out that a considerable proportion of patients show little or no steatorrhea following complete pancreatectomy or partial pancreatectomy in which pancreatic juice has been completely occluded by ligature.

Dr. Miller's suggestion that the relief of pain almost invariably reported following vagotomy for duodenal ulcer is presumably due to a lack of tonicity of the gastric wall is contradicted by our observation that the typical ulcer pain can be reproduced in all of its previous severity by the instillation of 200 cc. of 0.5 per cent hydrochloric acid solution into the stomach during the first five to ten days following vagotomy.[5] It is at this period when the depression in gastric motility is most profound. Incidentally, this observation indicates that vagotomy does not anesthetize the stomach through deprivation of its sensory nerve supply and that consequently there need be no fear of a painless recurrence of ulcer or painless perforation.

I am disappointed that Dr. Miller has called attention to the reports from those clinics only where the results of vagotomy have been more or less unsatisfactory. He has not referred to this clinic or to the Cleveland Clinic where the largest series of cases have been accumulated and where the results have been found to be more favorable

[3] Adams, W. E. and Phemister, D. B. Carcinoma of lower thoracic esophagus; report of successful resection and esophagogastrostomy, *J. Thoracic Surg.*, 7: 621, 1938.

[4] Brunschwig, A. *Surg., Gynec. & Obst.*, 88: 266, 1949.

[5] Dragstedt, L. R., Woodward, E. R., Harper, P. V., Jr. and Storer, E. H. Mechanism of relief of ulcer distress by gastric vagotomy. *Gastroenterology*, 10: 200, 1948.

than those secured by subtotal gastric resection.

Dr. Miller suggests that vagotomy alone is contraindicated in gastric ulcer because of the difficulty in ruling out a malignant lesion. I concur with this conclusion only for those lesions in the lower half of the stomach where subtotal gastrectomy will suffice to remove the lesion and a sufficient margin of normal gastric mucosa to serve as a therapeutic measure should, on subsequent pathologic examination, the ulcer be found to be malignant. When, however, a partial gastrectomy is performed for an ulcer in the upper half of the stomach the line of transection comes so close to the lesion that nothing is accomplished in the way of therapy should subsequent examination establish the presence of carcinoma. Total gastrectomy for these high-lying lesions, although the only operation that offers any prospect of cure for carcinoma in this area, is not justified in the absence of a positive diagnosis of malignancy. The operative mortality is still too high and the digestive disability too great in the patients that survive. We have seen a number of these juxta-esophageal gastric ulcers in which malignant transformation could not be demonstrated, heal following vagotomy and gastroenterostomy in a remarkably short period of time.

It is true that six years is too short a time to permit final conclusions regarding the place of vagotomy in the therapy of peptic ulcer. Success seems to be dependent upon the ability of the surgeon to divide all the vagus branches to the stomach and to deal with the motor dysfunction in the immediate postoperative period. Routine posterior gastroenterostomy and decompression of the stomach have almost entirely eliminated difficulty with stasis in this clinic, but complete vagotomy has not yet been achieved in all cases. I am persuaded that the hypersecretion of acid gastric juice so uniformly present in duodenal and gastrojejunal ulcers is of neurogenic origin, and the healing of these ulcers following vagotomy with resultant removal of the hypersecretion indicates that vagotomy is sound from the standpoint of the etiology of the disease. It should be remembered that with this, as well as with other operative procedures, the clinical results improve as the surgeon gains in experience in performance of the operation and in postoperative care.

LESTER R. DRAGSTEDT, M.D.
University of Chicago
Chicago, Ill.

Clinical Studies

Use of Hyperimmune Antirabies Serum Concentrates in Experimental Rabies*

HILARY KOPROWSKI, M.D., JAMES VAN DER SCHEER, CH. E., AND JACK BLACK
Pearl River, New York

RABIES is the only known viral disease of humans which, once the signs appear, is uniformly fatal. All efforts since 1885 to develop a protective treatment after exposure have not gone much beyond the classic Pasteur procedure, and the use of the original Pasteur type of vaccine or its numerous modifications has constituted the main bulwark against rabies.

However, a physician confronted with an individual who has been bitten by an animal suspected to be rabid is faced with two problems: What are the chances, especially in case of severe bites, that the patient's life will be saved by the Pasteur treatment and, second, what are the chances that the patient will not become a victim of neuroparalysis which sometimes accompanies Pasteur treatment? Judging from reviews published in the past[1,2,3] no clear-cut conclusions can be drawn about the general applicability of antirabies vaccination after exposure. The consensus is that Pasteur treatment is futile for individuals so severely bitten by rabid animals that the incubation period is shorter than thirty days.[3,4] Evidence obtained by some authors, as Proca and Bobes[3] and Dodero,[5] appears to give support to the opinion of Nitch[6] that drastic intensive antirabies treatment by vaccination may result in a fatal outcome after a much shorter incubation period than in untreated humans. Although Remlinger and Bailly[7] have confuted this postulate, the view that Pasteur treatment is of little or no avail in case of severe exposure continues to remain unchallenged. Furthermore, evidence points overwhelmingly to the fact that Pasteur treatment is associated with the so-called neuroparalytic accidents, which often present a picture of severe disease with extensive involvement of the central nervous system ending in death in some cases. The incidence of neuroparalytic accidents, calculated by Greenwood[2] as one in 5,814 vaccinated individuals, has been observed by Redewill and Underwood[8] to be one in 1,194 treated persons in Los Angeles County during the 1940-1945 period. Postvaccinal paralysis, which is paralleled by the same type of condition in dogs submitted to antirabies vaccination,[9] is particularly tragic when individuals who only presumably had been exposed to rabies infection die as a result of vaccine treatment.

These were the considerations which prompted the studies reported herein. The two main approaches were: (1) to develop, if possible, a substitute for or an adjunct to the Pasteur treatment; (2) to attempt the identification and subsequent elimination of the paralitogenic factor in normal brain tissue responsible for the neuroparalytic accidents accompanying vaccination. It is not the purpose of this report to summarize the studies and the negative results obtained so far in experiments to determine the factor or factors responsible for the paralitogenic properties of normal brain tissue; the report will be limited to the description of results obtained with the use of antirabies serum.

* From the Section for Viral and Rickettsial Research, Lederle Laboratories Division, American Cyanamid Company, Pearl River, N.Y.

Studies on the protective power of serum in rabies have been conducted ever since the original work of Babes and Lepp[10] appeared, and an adequate historical summary of the problem may be found in the report by Habel.[11] It may suffice to point out that evidence in favor of serum treatment of exposed animals[12] was as strong as negative evidence.[13] In cases of human prophylaxis Proca and Bobes[3] and Shortt et al.[14] were favorably impressed by the role of serum as an adjunct to the customary vaccination procedure. More recently Hoyt et al.[15,16] and Habel[11] found serum efficacious in protecting animals injected with rabies virus.

The present experiments were planned to parallel events occurring in nature, that is, first exposure of the animals to the virus then treatment with either serum or vaccine, or both. That the preliminary results with serum protection[17] were successful was due largely to the fact that in screening laboratory animals for the work, hamsters were found to be ideally suited for this type of research.

MATERIAL AND METHODS

Antirabies serum was obtained from either rabbits or sheep hyperimmunized by replicate injections of the egg-adapted Flury strain[18] and rabbit-brain fixed viruses. The animals were bled at regular intervals, the plasma pools were fractionated by sodium sulfate precipitation and the fractions containing the gamma-globulin concentrated, or the serum pools were fractionated by methanol precipitation and again the gamma-globulin fraction concentrated. In both instances the concentrate was adjusted to contain 7 per cent protein.

In neutralization tests, in which mixtures of serial tenfold dilutions of fixed strain of rabies virus and aliquots of dialyzed concentrates were injected intracerebrally in mice, the neutralization index of the serum concentrates was found to be about 10,000 LD_{50}, no difference being observed between the concentrates obtained from the rabbits or sheep.

To test the protective power of the serum concentrates hamsters (weighing 75 to 90 gm.) or guinea pigs (weighing 400 to 450 gm.) were inoculated intramuscularly with a suspension of canine salivary gland infected with the NYC strain of rabies virus.[17] Unless otherwise stated, hyperimmune antirabies serum was administered to the animals in a single subcutaneous injection of 1.0 ml. per animal twenty-four hours after the virus injection.

For the comparative test of the protective power of serum and of phenolized vaccine preparations, the animals were treated each day for fourteen consecutive days with 0.5 ml. of the respective dilutions of vaccine, the first injection being given usually twenty-four hours after the virus inoculation.

In all of the experiments an equal number of untreated, virus-infected controls were included. All animals were observed for five months after the virus inoculation and then were rechallenged with street virus.

RESULTS

Effect of Route of Inoculation upon Susceptibility of Hamsters to Infection with Street Virus. It has been mentioned above that the study on serum protection in experimental rabies was greatly aided when it was observed that the Syrian hamster was highly susceptible to street virus.

In order to determine more accurately the infectivity of street virus preparation for hamsters a large pool of a suspension of canine salivary glands was kept frozen and on several occasions was titrated in hamsters in fourfold dilutions. The animals were injected either bilaterally into the masseter muscles or unilaterally into the gastrocnemius with 0.1 ml. of respective virus dilution per hamster. Results of three representative titrations of the same virus pool are shown in Table 1. In the first two experiments the animals were inoculated into the masseter muscles; in the third the virus was injected into the leg muscles. The last column of the table shows the LD_{50} of the same viral preparations obtained in mice inoculated intracerebrally. It is apparent that with the masseter route of inoculation higher LD_{50} titers were obtained than with the leg-muscle route. Moreover, titers obtained by the masseter route were almost equal to those observed in mice inoculated intracerebrally. In

further studies it became evident also that a higher concentration of antiserum was needed in order to prevent the occurrence of rabies in hamsters inoculated by the masseter route than in those inoculated into the leg muscles.

TABLE I
TITRATION OF STREET RABIES VIRUS IN HAMSTERS

Route of Inoculation	Mortality Ratio of Hamsters						LD_{50} Titer	
	Log of Virus Dilution:						Hamster	Mouse
	2.2	2.8	3.4	4.0	4.6	5.2	I.M.*	I.C.†
Intramasseter		8/8	8/8	8/9	8/9	3/9	5.00	5.85
		10/10	10/10	8/10	2/9	3/8	4.45	4.45
Leg muscle	10/10	5/5	4/5	2/5	0/5	0/5	3.80	4.60

* I.M. = intramuscular
† I.C. = intracerebral

Comparative Protection of Rabies-infected Hamsters Treated with Antiserum or with Phenolized Vaccine. In this experiment hamsters were injected into the leg muscles with dilutions of canine salivary gland infected with street virus and then were treated either with antiserum alone or received each day for fourteen consecutive days 0.5 ml. of respective vaccine dilution. To date several experiments have been completed but not in a single instance has any beneficial effect been noted from vaccine treatment.

Simultaneously titrations of the virus pool were carried out in hamsters which showed that the 1:160 dilution contained 40 LD_{50} of virus while the 1:320 dilution contained 20 LD_{50} of virus.

Antiserum concentrates were administered in serial twofold dilutions in a single injection twenty-four hours after inoculation of the virus. For the vaccine treatment, also instituted twenty-four hours after exposure, two dilutions of Semple type vaccine were employed, one in 1:5000 dilution which on weight basis corresponded to the dose employed in humans, and in 1:20 dilution which is the actual concentration used in many instances for Pasteur treatment of humans. It is needless to add that the vaccines employed throughout the experiments met the minimal necessary requirements of antigenicity set by the National Institutes of Health.[18]

The results of the experiment summarized in Table II indicate that one injection of antiserum, even in the 1:16 dilution, protected a majority of the animals infected with the 1:160 dilution of virus, and that antiserum in 1:32 dilution showed the same protective power for the animals infected with the 1:320 dilution of virus. In contrast, treatment with the Semple type vaccine gave no evidence of protection whatsoever, as indicated by identical mortality ratios with the untreated control animals.

TABLE II
COMPARATIVE PROTECTION OF HAMSTERS TREATED WITH ANTISERUM OR VACCINE

Type of Protective Treatment	Dilutions	Mortality Ratio of Hamsters Infected with Virus Dilutions	
		1:160*	1:320†
Antiserum	1:2	1/10	
	1:4	2/10	
	1:8	2/10	
	1:16	4/10	1/10
	1:32	6/10	3/10
	1:64	10/10	5/10
Semple vaccine	1:20	10/10	10/10
	1:5000	10/10	10/10
Untreated controls		10/10	10/10

* Contained 40 LD_{50} of virus.
† Contained 20 LD_{50} of virus.

Comparative Protection of Hamsters with Antiserum Alone and Antiserum Followed by a Course of Phenolized Vaccine. In view of the consistently negative results obtained with the vaccine treatment of animals exposed to rabies, it was of interest to determine whether antiserum combined with vaccine treatment would give better protection than antiserum alone, or whether vaccine following the antiserum treatment would have a detrimental effect.

Hamsters were inoculated bilaterally into the masseter muscles with 1:640 dilution of street virus and then divided into six

experimental groups. Two groups were injected twenty-four hours later with undiluted antiserum concentrate, followed in one group twenty-four hours later with a course of fourteen injections of phenolized vaccine in the dilutions indicated in Table III. Two other groups of virus-exposed hamsters received one injection of undiluted antiserum concentrate seventy-two hours after exposure. This greater time interval was allowed to elapse since it had been observed in other experiments that such "timing" would protect about one-half the infected animals. Again hamsters in one of the groups were not treated further, whereas in the other group twenty-four hours later a course of fourteen injections of phenolized vaccine was started. Finally one group of hamsters was left untreated and the other received only vaccine treatment started twenty-four hours after virus exposure.

TABLE III
COMPARATIVE PROTECTION OF HAMSTERS TREATED WITH ANTISERUM AND VACCINE

Type of Protective Treatment Administered			Mortality Ratio of Hamsters Infected with 1:160 Dilution of Virus			
			Received vaccine:			
	After Infection (Hours)	After Serum (Hours)		1:20	1:200	1:500
Antiserum Followed by vaccine	24	24		4/10	3/9	6/10
Antiserum Followed by vaccine	72	24		4/10	5/9	6/10
Antiserum alone	24		1/10			
	72		4/8			
Vaccine alone	24			9/10	9/10	8/10
Untreated controls			8/10			

It may be noted from the data shown in Table III that when antiserum alone was administered twenty-four hours after infection, only one of ten hamsters died of rabies. If the same type of antiserum treatment was followed by a fourteen-day course of vaccine, the results were equivocal although more hamsters did die in the antiserum-vaccine treated groups. Thus it is possible that vaccine may have exerted some depreciative effect on antiserum therapy in hamsters.

When antiserum alone was administered seventy-two hours after exposure 50 per cent of the animals were protected but when the same type of antiserum treatment was followed by a fourteen-day course of phenolized vaccine, the results did not seem to be affected in either direction. Thus one may assume that the combined antiserum and vaccine treatment of hamsters exposed to rabies did not enhance the beneficial effect of antiserum given alone.

TABLE IV
COMPARATIVE PROTECTION OF GUINEA PIGS TREATED WITH ANTISERUM OR VACCINE

Virus Dilution	Type of Protective Treatment	Mortality Ratio of Guinea Pigs
1:160	Serum alone—1:8	4/10
	Serum (1:8) plus vaccine*	2/10
	Vaccine alone*	10/10
	Untreated controls	10/10

* 1:20 dilution of Semple type vaccine injected in 0.5 ml. amounts per animal for fourteen consecutive days.

Finally, it may be noted that the mortality ratio for hamsters subjected to vaccine treatment only did not differ from those of the untreated control group.

Comparative Protection of Guinea Pigs Treated with Antiserum and Vaccine after Exposure to Rabies. Since all of the above experiments were conducted in hamsters, it was of interest to ascertain what the response would be of other animal species to the above therapeutic procedure. Guinea pigs were inoculated bilaterally into the masseter muscles with a 1:160 dilution of canine salivary gland infected with street virus and then divided into four groups: one group, twenty-four hours after virus administration, was inoculated with 1:8 dilution of antiserum concentrate; another group received one injection of antiserum as above followed by a fourteen-day course of phenolized vaccine; the third group

received vaccine treatment alone; and the fourth was left as an untreated control group.

The results of this experiment shown in Table IV indicate that none of the animals receiving the vaccine course alone survived, but six of ten exposed animals were saved in the antiserum-group, and eight of ten animals by serum treatment followed by a course of vaccine.

Thus the above results indicate not only that vaccination of hamsters and guinea pigs with phenolized rabies vaccine preparations is of little avail but that the combination of antiserum followed by vaccine does not materially enhance the survival ratio of the exposed animals.

Effect of Delayed Administration of Antiserum in Hamsters. In most of the foregoing experiments antiserum was administered to hamsters twenty-four hours after virus exposure. Since in some instances the treatment of exposed human beings, because of technical difficulties, is delayed for more than twenty-four hours after exposure, it was imperative to study the effect of delayed administration of antiserum upon the course of rabies infection in hamsters.

Several experiments were performed in which antiserum was given to animals infected by the masseter route twenty-four, forty-eight, seventy-two hours and in one experiment as late as ninety-six and 120 hours after exposure. The results of these experiments indicated that for serum protection to be effective, there is a definite direct relationship between the amount of virus inoculated, the concentration of serum employed and the time interval elapsing between infection and administration of serum. If low concentrations of virus were employed followed by high concentrations of antiserum, treatment which would afford protection to about one-half of the exposed animals could be delayed even for seventy-two hours. Conversely, results of some of the preliminary experiments indicate that antiserum has little or no demonstrable protective effect if administered later than seventy-two hours after exposure.

Minimal Effective Dose of Antiserum. All of the foregoing experiments give results applicable to experimental work in animals. Since it was hoped that eventually the knowledge gained by laboratory experience could be applied to human prophylaxis, the proper dose of antiserum would have to be determined. Experiments were planned in which rabies-exposed hamsters or guinea pigs were treated with a single injection of serial twofold or fourfold dilutions of antiserum and the mortality ratios plotted against those obtained with untreated controls. In the first series of experiments the intramasseter route of virus inoculation of hamsters was employed and the effective dose of antiserum for hamsters, calculated on weight basis, was found to be very high, namely, 1.5 ml. per kg. of body weight. This dose was initially recommended and applied to humans in several cases of exposure to rabies but it may have been slightly overestimated because of the high degree of susceptibility of hamsters to street virus. It was, therefore, decided to duplicate the experiments in some other species and again guinea pigs were chosen. Groups of these animals as well as hamsters were infected by the intramasseter route with 1:160 dilution of street virus and treated twenty-four hours later with one injection of antiserum concentrate in 1:2 or 1:8 dilution, respectively. In addition the virus was titrated in guinea pigs and hamsters to determine the comparative susceptibility of the two species.

The results of the virus titrations summarized in Table V indicate that the LD_{50} titer of the virus was even higher in guinea pigs than in hamsters, and yet the same amount of antiserum seemed to display a higher protective power in the guinea pig than in the hamster, as evidenced by the fact that seven of the ten guinea pigs and only four of the ten hamsters were protected by the 1:8 dilution of antiserum. Should the 1:8 dilution of antiserum be considered the minimal effective dose for rabies-exposed guinea pigs then, calculated on weight basis, the effective dose of serum

concentrate in guinea pigs is 0.30 ml. per kg. of body weight, a value five times lower than that calculated for hamsters.

However, the intramasseter route of infection constitutes a very severe form of exposure which probably is never duplicated in nature in cases of human exposure to rabies. Consequently, attempts were made to recalculate the effective serum dose on the basis of experiments in which hamsters were infected with a moderate dose of virus by the leg-muscle route and then treated with serial dilutions of antiserum.

TABLE V

COMPARATIVE SERUM PROTECTION OF HAMSTERS AND GUINEA PIGS AFTER EXPOSURE TO STREET RABIES VIRUS

Serum* Dilution	Animal†	Mortality Ratio of Animals Infected with Virus Dilutions					LD_{50} Titer
		1:160	1:800	1:4000	1:20000	1:100000	
1:2	Guinea pig	2/10					
	Hamster	5/10					
1:8	Guinea pig	3/10					
	Hamster	6/10					
Controls	Guinea pig	10/10	6/6	6/6	6/6	4/6	$>10^{-5.00}$
	Hamster	10/10	6/6	6/6	6/6	1/6	$10^{-4.70}$

* 1 ml. per animal subcutaneously twenty-four hours after inoculation with virus.

† At time of inoculation: each guinea pig weighed 450 gm.; each hamster 75 gm.

Results of two such experiments are summarized in Table VI. In the first experiment (A) the protective power of serum concentrate of sheep origin was determined by titration in twofold dilutions against two dilutions of virus. In the second experiment (B) comparison was made between the protective power of antiserum of sheep and of rabbit origin in hamsters infected with a 1:320 dilution of virus. In experiment A there was little if any difference apparent in the protective power of serum when tested against the higher or lower dilution of virus. In experiment B the protective power of antiserum seemed to run parallel with only minor differences, regardless of the animal origin of the hyperimmune serum concentrate. If on purely theoretic grounds the minimal protective titers are calculated for both experiments, the sheep serum concentrate would yield a figure ranging between 1:32 and 1:64 dilutions, against 1:320 dilution of virus; recalculation of these titration results on weight basis would give 0.20 ml. to 0.40 ml. per kg. of body weight. If 0.50 ml. per kg. of body weight were chosen arbitrarily as the safer dose, it seems that this amount could be recommended for human beings in case of moderate exposure. Of course, this dose would apply to antiserum concentrates containing, as in the present experiments, protein at 7 per cent concentration. If the protein concentration would be doubled to reach the standard used in serum globulin for prophylaxis of measles, 0.25 ml. per kg. of body weight could be recommended.

TABLE VI

PROTECTIVE POWER OF ANTISERUM CONCENTRATES DETERMINED BY TITRATION AGAINST TWO DILUTIONS OF STREET VIRUS

Experiment	Virus Dilutions	Origin of Antiserum	Mortality Ratio of Hamsters Infected with Virus*							
			Treated with Dilutions of Antiserum†							Untreated Controls
			1:2	1:4	1:8	1:16	1:32	1:64	1:128	
A	1:160	Sheep	2/9	2/9	4/9	3/9	5/9	4/9		9/9
	1:320	Sheep			2/9	5/9	3/9	2/9		9/9
	1:640									7/9
	1:2560									4/9
	1:10240									2/8
	1:40960									0/8
B	1:320	Sheep	1/9		3/9		5/9	2/9	7/9	9/9
	1:320	Rabbit	1/9		1/8		3/9	1/9	8/9	9/9
	1:640									7/9
	1:2560									2/9
	1:10240									0/9
	1:40960									

* By leg-muscle inoculation.

† 1.0 ml. of the respective dilution of antiserum concentrate administered subcutaneously twenty-four hours after inoculation of virus.

Protective Power of Antiserum in Humans. Thus far antiserum treatment has been applied in twenty* cases of human beings who were treated either because of bites sustained from animals suspected to be

* The authors are indebted to Dr. Tom F. Sellers, Commissioner of Health, State of Georgia, and to Dr. E. J. Sunkes, Director of the Laboratory, State of Georgia Department of Public Health, for their kind permission to utilize some of their clinical data.

rabid, or probable exposure to rabies, or after a laboratory accident. Seven of the twenty patients were identified as definitely exposed, i.e., either the animal which inflicted the wound was found to be rabid or the laboratory material contained street virus. In all of these cases antiserum concentrate was administered intramuscularly in 1.0 to 1.5 ml. amounts per kg. of body weight. In all but two cases antiserum was administered within twenty-four hours after exposure. Only in one case, which twice received a full course of Pasteur treatment prior to the current exposure, antiserum alone was employed. In all other cases antiserum treatment was followed either by a short course of vaccine (3 doses of 2 ml. each of State of Georgia type of vaccine given on alternate days; seven-day course of Semple vaccine) or intensive vaccine treatment (twenty-one-day course of State of Georgia vaccine).

TABLE VII
NEUTRALIZATION TESTS OF SERA FROM INDIVIDUALS TREATED WITH EITHER ANTISERUM AND/OR VACCINE

Case	Protective Titer of Serum Obtained					
	Before Treatment	One Day after Serum Injection*	Days after First Injection of Vaccine†			
			3	7	14	30
T. J.	<1:2	1:50	1:65	1:70		1:55
75	<1:2			<1:2	1:4	
86	<1:2			1:4		
15					<1:2	1:3
124				<1:2	<1:2	
43				<1:2	1:16	

* Antirabies serum concentrate administered within three hours after exposure.

† Seven-day course of phenolized vaccine initiated twenty-four hours after exposure.

To date none of the patients has shown any signs of rabies. Although it is difficult, if not impossible, to evaluate critically data obtained in treatment of humans, attention may be drawn to two rather severely exposed cases. One, an animal attendant, was bitten by a rabid guinea pig which inflicted a severe penetrating wound on his left wrist. The animal was killed immediately and its salivary gland removed, triturated and titrated intracerebrally in mice. The results of the titration indicated that the LD_{50} titer of the street virus was $10^{-4.50}$ and thus one may assume that a severe exposure had occurred. The patient received 120 ml. of antiserum concentrate (1.5 ml. per kg. of body weight) four hours after exposure, followed twenty-four hours later by a course of phenolized Semple vaccine for seven consecutive days. To date, six months after exposure, no signs of illness have been observed.

In another instance a seventy year old woman was severely bitten by her own dog which inflicted five severe wounds on the palms of both hands. The brain of the animal examined at the Laboratory of the Georgia State Department of Public Health showed presence of Negri bodies. The patient received 100 ml. of antiserum (2 ml. per kg. of body weight) twenty-five hours after exposure, followed by an intensive course (twenty-one days of 2 ml. daily) of State of Georgia rabies vaccine. To date, one year after exposure, the patient is in perfect condition.

An opportunity was afforded to gain some insight into the mechanism of antiserum protection by an accidental laboratory exposure to street virus. Within three hours after exposure Case T. J. was given antirabies serum (1.5 ml. per kg. of body weight) followed by a seven-day course of Semple vaccine. He was bled at regular intervals and his serum submitted to neutralization test. In this test serial fourfold dilutions of serum were mixed with a dilution of fixed strain of rabies containing 100 LD_{50} of virus. The mixtures were incubated and injected intracerebrally into mice. In addition to serum samples obtained from Case T. J., who received both antiserum and a short course of vaccine, serum samples were secured from five individuals who had been given a seven-day course of vaccine treatment after exposure but no antiserum.

The results of the neutralization tests shown in Table VII indicate that in the case of T. J. the serum sample obtained twenty-four hours after administration of the antiserum concentrate, and before the first injection of vaccine, showed a definite level of antibodies as indicated by the 1:50 minimal protective titer. This level of serologic immunity was maintained throughout the entire vaccination period, the same titer being obtained thirty days after initiation of treatment.

In contrast, the level of serologic immunity in the sera of individuals who were given only a course of vaccine treatment remained very low and the antibody response, if any, was very slow as compared to Case T. J.

Thus it may be concluded that antirabies serum concentrate induces a quick immunologic response in the treated individual, in contrast to antirabies vaccination to which the response is of much slower order.

Should Antiserum Be Used Alone or in Conjunction with Vaccination? The foregoing data seem to indicate quite clearly that vaccination of hamsters or guinea pigs with phenolized rabies vaccine preparations is of little avail after exposure. These results substantiate the negative results obtained in the past by various workers who tried to protect animals after exposure with vaccine treatment alone.[20] In contrast, the antiserum concentrate seemed in all instances to exert a definite protective power after exposure. Can a parallel be drawn between the results obtained in the present study in experimental animals and events occurring in nature in cases of humans exposed to rabies? The following considerations should be weighed.

In hamsters and guinea pigs the incubation period of experimental street rabies is thirteen to twenty-two days. Only very rarely will an animal show signs of illness later than thirty days after exposure, and the statistically insignificant number of such instances does not permit evaluation of any form of treatment. Inasmuch as an incubation period of rabies in humans of less than thirty days occurs only in severely exposed cases, it is not possible to duplicate in hamsters the sequence of events occurring in humans after a moderate or light exposure and, therefore, caution should be exercised before condemning the Pasteur treatment for humans despite the lack of supporting experimental evidence in animals.

Moreover, it should be mentioned at this point that in experiments in which the effects of antiserum alone, versus antiserum plus vaccine treatment were compared, there were a few instances in the antiserum-treated group of hamsters in which death occurred after a greatly prolonged incubation period, up to two to three months, and conversely, in the antiserum plus vaccine treated groups only rarely did any deaths occur among the hamsters beyond an incubation period of forty-five days. Thus in order to give Pasteur treatment benefit of the doubt, and to the antiserum the benefit of preliminary extensive trial in human rabies prophylaxis, it may be advisable that antiserum treatment for the time being, at least, be employed in conjunction with vaccine in all types of rabies exposures. It should be understood, however, reasoning along the same line, that protection of an individual after severe exposure lies only in the treatment with antiserum and not in vaccination since, as indicated by the results of the neutralization tests with human sera, only after antiserum treatment and not after vaccination does the exposed individual react with a quick establishment of serologic immunity.

Furthermore, if antiserum treatment in conjunction with vaccination should be considered, the course of the latter may be considerably shortened and, theoretically at least, the chances of occurrence of post-vaccinal paralysis would thereby be decreased with the diminished number of antigenic stimuli administered with each injection of normal brain substances which constitutes the menstruum employed in vaccines. For instance, a course of seven injections of antirabies vaccine may be

considered as sufficient in conjunction with antiserum treatment in lieu of the fourteen-day or twenty-one-day course.

Finally, antiserum should be quite valuable in those cases of human exposure in which either previous Pasteur treatments[21] or general allergic status of the individual[22] may be considered as predisposing factors for the development of postvaccinal neuroparalysis.

SUMMARY

Hyperimmune antirabies serum concentrates have been prepared in rabbits and sheep.

One injection of antiserum exerted a definite protective effect in hamsters and in guinea pigs which had been infected twenty-four hours previously with street virus. In contrast, a course of fourteen injections of phenolized rabies vaccine instituted twenty-four hours after exposure failed in all instances to protect the exposed animals from rabies.

A combined antiserum plus vaccine treatment of exposed hamsters seemed neither to enhance nor to decrease the protective power of antiserum administered alone.

An effective protective dose of antiserum has been calculated for guinea pigs and hamsters, and a tentative dose of 0.5 ml. per kg. of body weight has been suggested for use in humans after moderate exposure (twenty-four hours after exposure).

Several cases of antiserum treatment of humans exposed to rabies have been described and discussed.

In a general discussion of the problem the conclusion was reached that antiserum seems to have definite value and should be applied in every case of exposure to rabies, in conjunction with a short course of vaccine treatment.

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Tuberculous Peritonitis Treated with Streptomycin*

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PERITONITIS is a relatively uncommon manifestation of tuberculosis. In a recent report of the Streptomycin Committee of the Veterans Administration twenty-seven cases of tuberculous peritonitis represented only 0.97 per cent of a total of 2,780 patients with various types of tuberculosis treated with streptomycin.[1] In a report from the sanatorium "El Peral" it is stated that fifty-two or 1.17 per cent of a total of 4,426 patients admitted to the sanatorium had tuberculosis of the peritoneum. The incidence of tuberculous peritonitis varies between 1.25 and 16 per cent according to statistics based on postmortem studies of tuberculous individuals. This would suggest that peritoneal involvement may be more frequent than is recognized clinically.[3–7]

In spite of the relative rarity of the disease, publications discussing its manifestations, prognosis and therapy are numerous. Hertzler reviewed the literature in 1919[8] and called attention to the fact that while some of the earlier authors[9–11] were extremely pessimistic regarding the prognosis of tuberculous peritonitis, others[12–16] recognized that recovery was possible and prognosis depended at least in part on the presence or absence of co-existing lesions, especially of pulmonary tuberculosis. After Wells' original observation of recovery of a case of tuberculous peritonitis following laparotomy[5,17] and after König's publications in 1884, 1890 and 1892[18–20] there was a striking increase in the number of recoveries reported and surgical procedures became and remained accepted therapy for tuberculous peritonitis.[5,21–30] Paracenteses were combined with drainage,[31] saline irrigation[32] and injection of air or oxygen.[33,34] Laparotomies were performed for diagnostic reasons, for the purpose of exposing the abdominal contents to air or direct sunlight, for removal of foci of infection, especially in female patients, and for relief of intestinal obstruction. These operations have been combined with application of antibacterial agents such as iodoform,[19] intraperitoneal saline infusions[29] and intraperitoneal oxygen insufflation.[29,35,36]

The importance of medical management with rest, fresh air and diet needs no emphasis.[2,7,28,29] A large number of medications and procedures have been added to these general measures. Medications such as tuberculin,[37,38] cod liver oil, calciferol, hypophosphates, creosote,[8,39] collodion,[40] calcium,[29] tincture of iodine,[41] mercury[42] and gold salts[43] have been used by various authors.

Medical and surgical treatment have been combined with various types of radiation therapy. To the use of x-ray therapy[26,44–46] were added heliotherapy,[28,29,47,48] artificial radiation using the spectrum from infra-red to ultraviolet[2,28,29,47,49,50] and diathermy.[51]

Hinshaw et al. in 1946 and 1947[52,53] were the first to report on streptomycin therapy of tuberculous peritonitis. They stated that encouraging results had been obtained with

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streptomycin in their series of various types of tuberculosis which included patients with tuberculous peritonitis. Forlini et al.[54] had good results in four gynecologic cases in which streptomycin was given intraperitoneally as well as parenterally. Mace and Maryanov,[55] Perlstein and Gebauer,[56] Dickman[66] and Jellinek[68] reported excellent early results of streptomycin therapy of tuberculous peritonitis.

This paper is a report on the response of tuberculous peritonitis to streptomycin therapy as observed in twenty-six patients each of whom was treated with this antibiotic in various Veterans Administration hospitals. Two of these patients were treated by the authors. The abstracts or the complete clinical records of the remaining twenty-four cases were sent to them by various Veterans Administration hospitals whose support and continued cooperation in this joint study we gratefully acknowledge. Three additional cases will be reported shortly but will be separated from the larger group because the main therapeutic problem in these cases was draining sinuses following exploratory laparotomy for tuberculous peritonitis rather than peritoneal symptoms.

There were one white female, five white male and twenty colored male patients in the series. The age in the twenty-six cases ranged from nineteen to forty-three, with fourteen patients between twenty and thirty and four patients between thirty and forty years of age. On admission ten patients appeared acutely ill, five were emaciated, appearing chronically ill, and the remaining eleven were in fairly good general condition.

The diagnosis of tuberculous peritonitis was established by history, symptomatology and clinical findings and confirmed by surgical, bacteriologic and histologic findings and by demonstration of tuberculous lesions elsewhere. In only one patient of this series could a family history of tuberculosis be elicited.

In eleven of twenty-six patients abdominal symptoms of three days' to one year's duration were the first indication of a tuberculous infection. In eight of the twenty-six patients the diagnosis of tuberculosis had been made prior to admission to the hospital. One of these eight cases had been diagnosed as tuberculous peritonitis four years previously by laparotomy and demonstration of acid-fast organisms; the other seven patients had extraperitoneal tuberculosis. The remaining seven gave histories of recurrent abdominal symptoms, ascites, weight loss, "pleurisy," pleural effusion, pericarditis, pericardial effusion or hemoptysis which must be regarded as highly indicative of a preceding tuberculous infection. Four patients had no abdominal symptoms on admission, but the symptoms developed under observation. Duration of known or suspected tuberculous involvement varied from three months to four years, whereas abdominal symptoms had existed for two weeks to three years.

SYMPTOMS AND CLINICAL FINDINGS

The symptoms and clinical findings encountered in this group of patients were in agreement with those reported elsewhere in the literature.[2,5,7,27,29,57,58] (Table I.) Symptoms and findings were not always present on admission. In some cases they were elicited from the history or developed under observation. Fever was found in the majority of patients and in many of them had been present for many weeks or months. Onset of abdominal symptoms was acute in nine and insidious in ten patients. In the remaining seven there was a tendency to recurrent episodes of varying frequency, severity and acuteness over a period of months or years, most of the patients feeling chronically ill but two of them being asymptomatic in the interim between attacks. Although abdominal pain and swelling, nausea, vomiting and anorexia, when present, were consistent complaints, diarrhea and constipation were noted only for short periods of time and frequently subsided spontaneously. Abdominal pain was described by several patients as cramp-like pain occurring at intervals, often more pronounced at night.

Ten of twenty-six patients complained of cough. In six this could be attributed to coexisting pulmonary or pleural involvement. One of these six had rales in both bases without consolidation or x-ray evidence of tuberculosis. Cough and rales disappeared as ascites ceased to accumulate.

In two cases with considerable ascites and in two without demonstrable ascitic fluid no chest abnormality could be found.

Shortness of breath was a complaint of seven patients. Three had pleural effusions; one of these three had in addition electrocardiographic changes indicative of pericardial involvement. In two patients accumulation of ascitic fluid resulting in increased subdiaphragmatic pressure could explain the shortness of breath. In two patients, however, there was shortness of breath without the presence of ascites or demonstrable chest abnormality.

Of the five patients complaining of chest pain, two had evidence of coexisting pericarditis, one gave a history of pericarditis, one had a pleural effusion and in one no explanation of the chest pain could be advanced.

Occurrence of joint pain as the initial symptom deserves comment. In one patient the combination of joint pain, shortness of breath, precordial pain and recurrent ascites led to the diagnosis of rheumatic heart disease and the patient was treated as such for almost one year before the diagnosis of tuberculous peritonitis was established.

Distention varied from moderate to severe in the individual cases. Abdominal tenderness was present in seventeen cases and was described as marked in two, moderate in eight and slight in seven patients. Tenderness was generalized in seven cases and localized in the para-umbilical area, lower abdomen, epigastrium or right upper and lower quadrant in ten cases. In nine patients no abdominal tenderness could be elicited. In several patients there was a striking lack of correlation between presence and degree of tenderness and the degree of actual peritoneal involvement as demonstrated by laparotomy.

In several patients in whom ascites had been present at some time during the course of the disease, fluid was not found at laparotomy. In one case one year had elapsed between paracentesis and laparotomy. One patient was explored seventeen days after paracentesis and only gelatinous, yellowish green exudate but no free fluid was encountered. One patient had had two successful paracenteses; two weeks later paracentesis yielded only some greenish exudate and at operation one month later neither free fluid nor exudate was found. In one case peritoneal fluid had been obtained three times before streptomycin therapy was started. A peritoneoscopy was performed ten days after initiation of therapy. There were numerous adhesions and fibrinous exudate but fluid was not encountered nor were tubercles seen. It appears then that quite frequently the accumulation of ascitic fluid may cease spontaneously and rapidly and that formation of fibrinous or gelatinous exudate may represent the in-

TABLE 1
SYMPTOMS AND CLINICAL FINDINGS IN SIX SERIES OF CASES OF TUBERCULOUS PERITONITIS

	Hamman 1908[2,3]	Faulkner and Everett 1930[3] Gyn. Cases	McPhedran and Peacock 1933[27]	Stubenbord and Spiess 1938[29]	Barrow 1943[38]	Wichelhausen and Brown 1949
No. of Cases in Series	150	187	21	257	67	26
	%	%	%	%	%	%
Fever	90	76	..	17	82	92
Chills	5	...	..	.....	..	23
Pain	69	87	76	72	75	88
Weight loss	41	61	14	19	77	85
Diarrhea	22	7	..	15	..	42
Vomiting	28	27	24	30	32	38
Nausea	34	33	..	4		35
Abdominal swelling	15	...	42	66	..	31
Anorexia	.....	...	28	7	..	27
Constipation	32	42	..	23	..	23
Fatigue	.....	...	19	20	..	19
Night sweats	18	...	..	.....	..	12
Cough	31	26	29	10	..	38
Shortness of breath	20	...	..	.....	..	27
Chest pain	7	...	..	.....	..	19
Headache	7	...	..	4	..	12
Hemoptysis	.....	6	..	.....	..	4
Joint pain	.....	...	..	.....	..	4
Distention	.....	...	38	61	82	69
Tenderness	29	...	43	27	71	65
Ascites	41	44	24	35	65	62
X-ray changes gastrointestinal tract	.....	...	..	.....	..	25*
Rigidity	16	...	..	12	15	31
Draining sinus of abdominal wall	.....	...	..	3	..	23
Abdominal mass	37	...	9	27	..	23
Intestinal obstruction	2.6	...	..	.....	..	15
Hernia	.....	...	..	1.5	..	8
Palpable liver	11	...	..	3	..	8
Palpable spleen	2	...	..	.....	..	4

* Only 16 of 26 cases were studied

termittent stage between free fluid and adhesions.

Hernias were present in two patients. In one case an umbilical hernia was an incidental finding. In the other patient, however, an inguinal hernia was the presenting symptom which brought him to the hospital and the diagnosis of tuberculous peritonitis which had not been suspected before operation was made at the time of herniorrhaphy.

Four patients presented the clinical picture of intestinal obstruction. One patient was described as having a partial intestinal obstruction and one as having mild functional obstruction, with gastrointestinal x-rays showing no intrinsic lesion but considerable segmentation of the ileum. The third patient (Case 8) had had a diagnostic laparotomy in 1943. He continued to have repeated attacks of vomiting, fever, chills and constant weight loss over a number of years. During several hospitalizations the clinical diagnosis of intestinal obstruction was made but x-ray findings did not support such a diagnosis. It was only after four years that obstruction of the small bowel became demonstrable by x-ray. Obstruction was relieved by symptomatic treatment only to recur after six months at which time x-ray studies showed an increase in the process previously noted. The fourth patient gave only a four-week history of epigastric pain which occurred shortly after eating and was relieved by vomiting which became the major symptom. X-ray examination revealed a dilated, atonic stomach with almost complete pyloric obstruction, and diagnosis was made of a duodenal ulcer with scarring and obstruction. Operative findings were thickening of the wall of the pylorus which, when opened, revealed no ulcer, and thickening of the wall of the stomach associated with adhesions producing obstruction. There were innumerable adhesions throughout the entire abdominal cavity and numerous nodes scattered over the intestines. Lymph node biopsy revealed tuberculous lymphadenitis; acid-fast organisms were demonstrated in the gland. These findings were remarkable in view of the fact that on admission the abdomen was soft and flat, there was no tenderness nor were masses or organs palpable. Temperature was normal, white blood cells 8,200 and sedimentation rate 15 mm. /hr. uncorrected. Physical findings on admission nineteen days before laparotomy were minimal and an admission diagnosis of "peptic ulcer, with functional overlay" was made. (Table v, Fig. 3.)

X-ray studies of the gastrointestinal tract were performed in sixteen cases. Barium enemas were given to eight patients, with negative reports in seven. In one case there was evidence of a mass encroaching on the sigmoid as well as the cecum (Case 8). Gastrointestinal series were done in sixteen cases and normal findings reported in twelve of them. Three of the remaining four cases have already been described under intestinal obstruction. Marked pylorospasm, incomplete filling of the duodenal cap and distortion of the duodenal bulb were revealed in the fourth case. No ulcer crater was demonstrable. The second portion of the duodenum was grossly distorted, spastic and contracted, producing an irregular string-like appearance.

Draining sinuses of the abdominal wall were present in six cases. One developed following paracentesis, the other five after exploratory laparotomy.

Physical and x-ray findings were supported by surgical, bacteriologic and histologic evidence of tuberculous peritoneal involvement as well as by demonstration of tuberculosis in other locations. (Table II.)

It will be noted that laparotomies were performed in twenty of twenty-six patients and that two additional patients were subjected to peritoneoscopy. In twenty-one of these twenty-two cases there was gross evidence of tuberculous peritonitis. One patient had been operated upon two years prior to admission. At that time the diagnoses of tuberculosis of the right ovary and tuberculous salpingitis were established. (Table III.)

Acid-fast organisms could be demonstrated in material from the abdominal

cavity in only seven cases. In four instances guinea pig inoculations and/or cultures were positive; in three the organisms were demonstrated in biopsy sections only. A histopathologic diagnosis of tuberculosis was made in twenty cases and in nine of these caseation necrosis was noted. In only five of the cases was the histologic diagnosis substantiated by demonstration of acid-fast organisms. It is recognized that the finding of tubercles with or without caseation necrosis provides only suggestive evidence of a tuberculous infection. If, however, the histopathologic findings are evaluated together with the medical and surgical data, there can be little doubt regarding the diagnosis of tuberculosis in these cases.

In four cases neither bacteriologic nor histologic evidence of a tuberculous infection could be obtained from abdominal specimens. Three of these patients had tuberculosis elsewhere. One case with peritonitis, pleural effusion and pericarditis is included in this series. Good response to streptomycin therapy supported the clinical diagnosis in this case.

TABLE II

ESTABLISHMENT OF DIAGNOSIS

Case No.	Peritoneum					Evidence of Tuberculosis Elsewhere						
	Laparotomy	Peritoneoscopy	Acid-fast Organisms: Ascitic Fluid	Acid-fast Organisms: Biopsy	Biopsy Tb.	Present	History	Clinical	X-ray	Biopsy	Acid-fast Bacilli	Postmortem
15	✓	..	+	+	+	✓	✓	✓	✓	..	+	..
16	✓	..	+	−	+	✓	..	..	..	..	+	..
1	..	✓	+	0	0	✓	✓	✓	✓	..	..	..
14	..	..	+	0	0	..	..	✓*	✓*	..	+*	..
19	✓	..	0	+	+	✓	✓	✓	✓	..	..	..
22	✓	..	0	+	+	..	..	..	..	..	..	..
8	✓	..	0	+	+	..	..	..	..	..	..	..
10	✓	..	0	−	+	✓	..	✓	✓	✓	+	..
12	✓	..	0	−	+	✓	✓	✓	..	✓	+	✓
11	✓	✓	−	−	+	✓	..	✓	✓	..	+	..
6	✓	✓	−	−	+	✓	..	✓	✓	..	..	..
17	✓	..	?	−	+	✓	✓	..	..	✓	..	..
20	✓	..	0	−	+	✓	✓	..	..	..	..	..
3	✓	..	0	−	+	✓	✓	✓	✓	✓	+	..
4	✓	..	−	−	+	✓	✓	✓	✓	..	+	..
26	✓	..	0	−	+	✓	..	✓	✓	..	+	..
7	✓	..	0	−	+	✓	✓	..	✓	..	..	..
13	✓	..	−	−	+	✓	..	..	✓	..	..	..
24	✓	..	−	−	+	✓	..	..	✓	..	..	..
23	✓	..	?	−	+	..	..	..	..	..	..	..
21	✓	..	0	−	+	..	..	..	..	..	..	..
5	✓	..	0	−	+	..	..	..	..	..	..	..
18	..	..	−	0	0	✓	✓	✓	✓	..	+	..
9	..	..	0	0	0	✓	✓	✓	✓	..	+	..
2	..	..	0	0	0	✓	✓	✓	✓	✓	+	..
25	..	✓	−	0	0	✓	..	✓	✓	..	..	..

+ —positive
− —negative
? —not studied
0 —material not obtained
* —pulmonary Tb. 2 years after Sm. (Sm. = streptomycin)

The extraperitoneal tuberculous manifestations encountered in this group of patients were miliary tuberculosis, pulmonary tuberculosis, pleural effusion, pericarditis, adenitis, draining sinus, abscess and genitourinary tuberculosis. Only five of twenty-six patients never showed tuberculous involvement other than peritoneal.

TABLE III

Operative Findings in 21 Cases	Frequency with Which Encountered
Minute nodules	
On peritoneum	15
Over small bowel	5
Over large bowel	3
Over liver	1
Adhesions	10
Matting of intestines	5
Matting of omentum	1
Thickened peritoneum	1
Free fluid	7
Fibrinous exudate	3
Gelatinous exudate	1
Enlarged mesenteric glands	6
Large mass	1
Thickening of pylorus	1

Routine laboratory studies were not remarkable and contributed little to the diagnosis. The absence of leukocytosis recognized by Hamman in 1908[57] as characteristic was noted in this series also. Leukocytosis of over 12,000 was found in only three of sixteen adequately studied cases. The absence of leukocytosis in the presence of fever and abdominal symptoms presented a diagnostic problem in two cases, with high agglutination titers against E. typhosa and S. schottmülleri. In one patient streptomycin was started only hesitatingly because of an initial leukocyte count of 2,500.

Faulkner[5] reporting on 187 cases of tuberculous peritonitis has stated that no symptomatic syndrome is characteristic of this disease. In this small series of twenty-six cases, twenty-six different admission and differential diagnoses were advanced. Many of the diagnoses could be quickly discarded after a few days of observation and preliminary study; however, when one reviews clinical records from twenty-two different hospitals, one is impressed by the frequency with which certain diagnoses were made by different observers. The diagnosis of the typhoid fever group has already been mentioned. Many of these patients presented the picture of an "acute abdomen" due to cholecystitis, acute appendicitis, ruptured appendix, pelvic abscess or a perforated ulcer, necessitating surgical interference. It is easily conceivable that dense adhesions such as are produced by this disease may eventually lead to intestinal obstruction. If symptoms of obstruction, however, develop quite suddenly after a short period of illness as was the case in one patient of this series, it seems unlikely, even in retrospect, that the proper diagnosis could be made without exploration. It would appear that in a certain percentage of cases exploration is unavoidable because of the acuteness or severity of abdominal symptoms. It was interesting that the diagnosis of an amebic abscess of the liver was an important diagnostic consideration in two patients who were subjected to extensive and prolonged studies before the diagnosis of tuberculous peritonitis was made by an exploratory laparotomy.

THERAPY

All patients in whom the diagnosis of tuberculous peritonitis had been made were subjected to streptomycin therapy as soon as the antibiotic was available. Therapy was initiated in all cases regardless of duration, type or extent of peritoneal or of coexisting extraperitoneal tuberculosis. In some cases therapy was begun on the basis of clinical criteria without waiting for completion of laboratory studies. Daily dosage of streptomycin varied between 1 and 3 gm. given intramuscularly in two to six divided doses. Total dosage per patient varied from 42 gm. to 254 gm. for a single course. (Table VI.) One of the four patients treated with two courses of streptomycin received a total of 349.2 gm. of streptomycin. With these doses streptomycin blood levels between 1.25 and 40 micrograms were obtained. It is of interest that in one patient whose blood levels varied between 3.2 and 15.2 micrograms an ascitic fluid streptomycin

level of 11.7 micrograms was obtained, indicating that there is adequate diffusion of streptomycin into the abdominal cavity.

Duration of therapy varied between twenty-one and 137 days but one of the patients who received two courses of streptomycin had a total of 164 days of treatment.

TABLE IV
RESPONSE TO STREPTOMYCIN THERAPY TWENTY-SIX CASES

	During Course of Disease	At Start of Sm. Therapy	On Completion of Sm. Tnerapy	Remarks
Fever	24	21	3	1 new lesion developing elsewhere under Sm.; 1 temporary response, relapse, subsequent death; 1 failure, subsequent death
Pain	23	23	6	4 minimal discomfort; 1 pain disappeared after Sm. was discontinued; 1 failure, subsequent death
Tenderness	17	17	0	.....
Rigidity	8	8	0	.....
Abdominal swelling	8	8	0	.....
Distention	18	18	1	New lesion developing elsewhere under Sm.
Ascites	16	11	0	.....
Abdominal Mass	5	5	0	1 additional patient developed mass under Sm.; this disappeared after discontinuation of Sm.
	1	1	1	Mass noted during relapse; no response to 2nd course of Sm.
Intestinal obstruction	4	4	0	1 gastrojejunostomy prior to Sm.
Draining sinus of abdominal wall	6	6	0	.....
Nausea Vomiting Diarrhea Constipation	Intermittent in most cases		3	1 nausea, vomiting; ceased after Sm. was discontinued; 1 persistent constipation; 1 occasional attack of vomiting, nausea, diarrhea; returned later with exacerbation.

One of the most striking and dramatic responses to streptomycin was subsidence of *fever*. (Table IV.) A temperature elevation was present in most cases at initiation of therapy and had persisted for many months in some of the patients. Twenty-four patients had fever during the course of their illness and twenty-one were febrile when streptomycin therapy was initiated. Eighteen became afebrile during or shortly after streptomycin therapy. In one case a low grade fever was present three months after cessation of therapy. This patient initially showed prompt subsidence of fever and abdominal symptoms but developed a new tuberculous lesion, cervical adenitis, while on streptomycin therapy. In another patient the temperature became normal under streptomycin but fever recurred after streptomycin was discontinued because of toxicity. The patient was not retreated and died six months later. In the other fatal case of this series defervescence was not observed at any time.

The temperature charts 1, 2 and 3 illustrate the typical response observed in most patients. (Fig. 1.) It will be noted in chart 2 that treatment with penicillin, sulfadiazine and emetine did not influence the temperature curve. Chart 3 illustrates that three surgical procedures, exploratory laparotomy, incision and drainage of an abscess of the abdominal wall and exploration because of a suspected subdiaphragmatic abscess, did not influence the course of the disease which responded promptly to streptomycin therapy. Defervescence occurred as early as four to seven days after streptomycin had been started but a critical fall of temperature within twenty-four hours was never observed. Chart 4 illustrates persistence of low grade fever in a patient with peritonitis, miliary pulmonary tuberculosis and pleural effusion. The fever subsided completely after discontinuance of streptomycin therapy. The patient remained asymptomatic during twenty months of follow-up observation. The continued fever in the case illustrated in chart 5 is difficult to interpret. This patient had no other manifestations of tuberculosis. He received penicillin in conjunction with streptomycin and we may have been dealing with drug fever caused by either penicillin or streptomycin rather than with failure to respond to streptomycin in the usual manner. Chart 6 shows the initial response and sub-

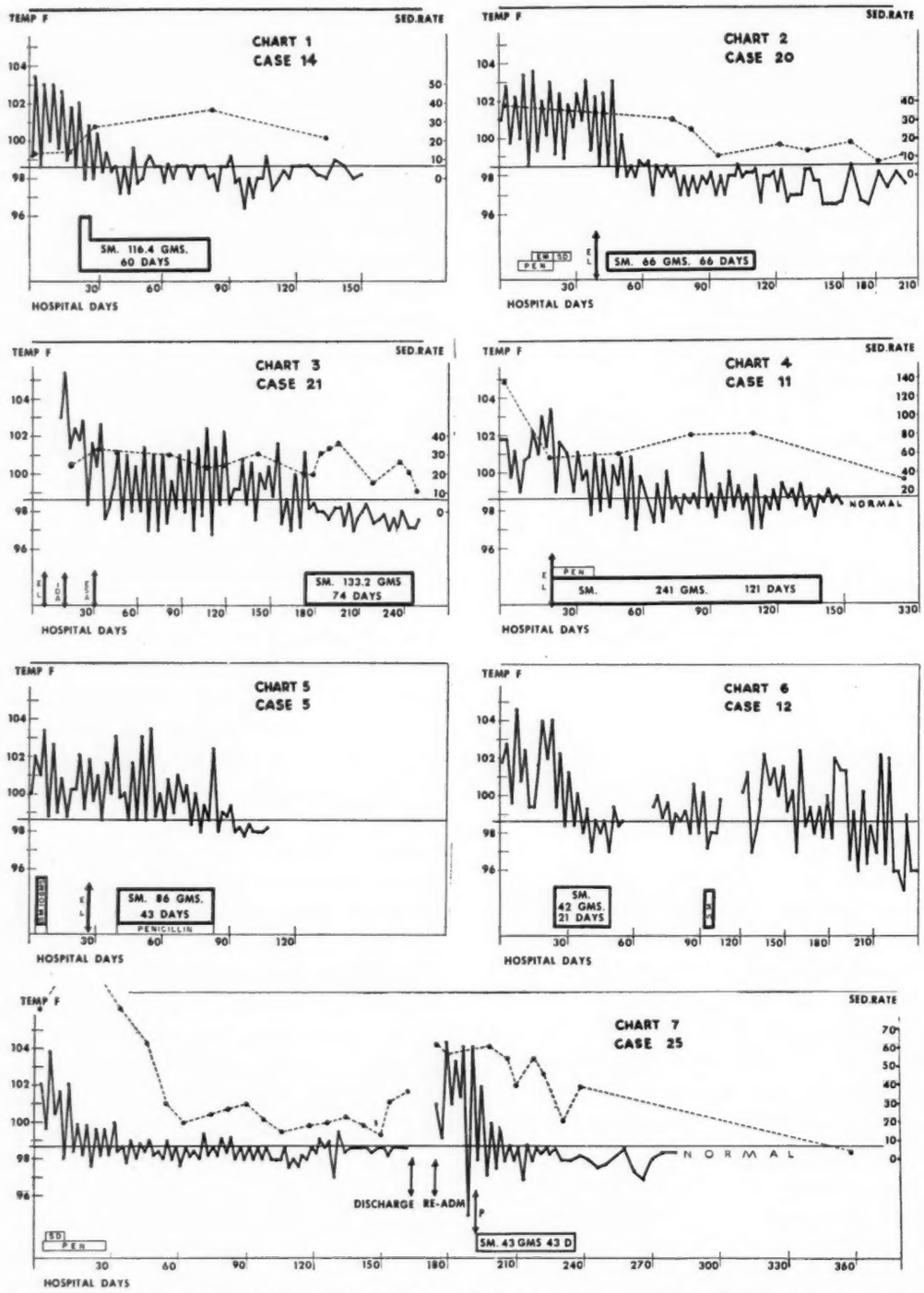

FIG. 1. Sm., streptomycin; Pen., penicillin; Sd., sulfadiazine; Em., emetine; EL, exploratory laparotomy; IDA, incision and drainage of abscess; ESD, exploration for subdiaphragmatic abscess; P., peritoneoscopy.

sequent relapse discussed (Case 12). Chart 7 is included to show that defervescence similar to that observed under streptomycin may occur without such therapy. On his first admission this patient had predominantly pleural and pericardial involvement, also some evidence of peritonitis. On the second admission the presenting symptoms were abdominal but pleural effusion and suggestive evidence of pericarditis were also present.

Data on sedimentation rates were available to us in only a limited number of cases and are difficult to compare because of the different methods used in various hospitals. It will be noted, however, that subsidence of fever was not always accompanied by a corresponding decline of the sedimentation rate. A few patients, in fact, showed a transient rise.

Abdominal pain, tenderness, rigidity, swelling and *distention* receded more gradually than the fever but most patients were much relieved after one to two weeks and relatively asymptomatic about one month after initiation of streptomycin therapy. (Table IV.)

Twenty-three patients had abdominal pain at the beginning of specific therapy. Twenty-one of these patients were relieved of pain under streptomycin therapy, seventeen being completely asymptomatic and four still experiencing minimal abdominal discomfort at the end of treatment. In one patient with pulmonary tuberculosis previously treated with pneumoperitoneum, abdominal cramps persisted while fever and ascites subsided promptly. Abdominal pain disappeared after streptomycin had been discontinued. In one fatal case with questionable response to streptomycin no relief of abdominal pain was noted.

At completion of therapy abdominal tenderness, rigidity and swelling were not demonstrable in any of the patients in whom they had been noted previously. Abdominal distention disappeared in the eighteen patients in whom it was found before therapy. In one patient, however, distention recurred at the end of therapy coincident with the development of a draining sinus in a cervical biopsy scar.

Although sixteen patients had evidence of *ascites* at some time during the course of their disease, this was present at initiation of therapy in only eleven patients. In ten of these eleven patients ascites disappeared within the first two to four weeks and in one only after six weeks of streptomycin therapy. The failure to reaccumulate ascitic fluid and the rapidity with which it was absorbed was quite remarkable in several patients. One patient who needed six paracenteses (850 to 3,840 cc.) within two weeks yielded no fluid on paracentesis ten days after streptomycin had been started and no further accumulation of ascites occurred.

In all patients in whom an abdominal *mass* was found prior to streptomycin this could not be felt after therapy. In one patient, however, a palpable mass developed in the left lower quadrant while the patient was under streptomycin therapy. It is conceivable that it had been obscured originally by pronounced distention. The mass disappeared after completion of streptomycin therapy. Another patient developed a mass during a relapse; this did not respond to the second course of streptomcyin therapy.

Six patients presented the complication of a *draining sinus* of the abdominal wall. In five the sinus had developed following laparotomy, in one case following paracentesis. All sinuses closed under streptomycin therapy, including a sinus in the one fatal case in which no other response to streptomycin was shown. One sinus that had closed under streptomycin therapy started to drain again after streptomycin had been discontinued but closed again without further therapy.

Four patients exhibited the clinical picture of *intestinal obstruction.* In one of the patients the obstruction had to be relieved by gastrojejunostomy prior to streptomycin therapy. The remaining three improved under streptomycin without surgical intervention.

The symptoms of *nausea, vomiting, diarrhea* and *constipation* occurred in episodes and were not always present just before initia-

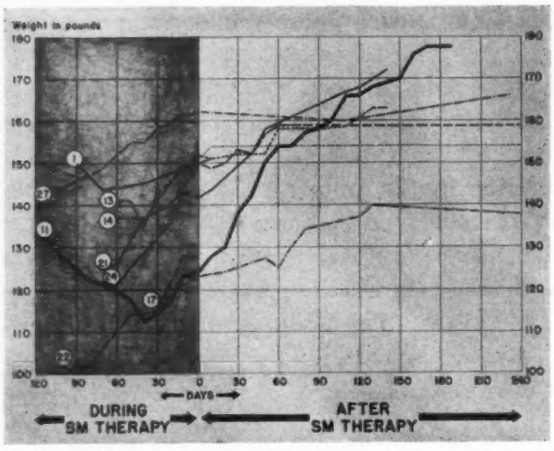

FIG. 2. Weight chart of nine patients during and after streptomycin therapy.

tion of therapy. In only three of the twenty-four surviving patients were any of these symptoms present at completion of therapy. One patient continued to have poor appetite, nausea, vomiting and abdominal cramps during the entire course of streptomycin therapy in spite of defervescence and disappearance of ascitic fluid. It was believed that the persistent symptoms might represent a toxic reaction and streptomycin was discontinued because of this. The patient became asymptomatic shortly after he had been taken off the drug. One patient continued to complain of constipation one year after cessation of streptomycin therapy. One patient who had had recurrent episodes and x-ray evidence of intestinal obstruction improved remarkably and the obstruction was not further demonstrable by x-ray. However, occasional mild attacks of diarrhea, nausea and vomiting persisted. He returned later with exacerbation and will be discussed in the paragraph on follow-up studies.

The consensus of all observers was unanimous concerning marked *general improvement* as evidenced by a feeling of well being, improved appetite and gain of weight and strength. Twenty-four of twenty-six patients, including one patient who relapsed and subsequently died, experienced a feeling of well-being and increased strength as early as one to two weeks after therapy had been started. This was particularly impressive in the emaciated, chronically ill patients but equally definite in the more acute cases. One patient failed to respond and one patient, described in the preceding paragraph, showed general improvement only after discontinuance of the drug.

Twenty-one of 26 patients showed increased appetite with subsequent *weight gain*, which was striking in many of the cases. (Fig. 2.) One patient gained as much as 66 pounds. The remaining five patients included two patients who had shown no loss of appetite or weight prior to institution of streptomycin therapy, the two fatal cases, and one patient in whom persistent anorexia was attributed to a toxic reaction to the drug and whose course was complicated by previous pneumoperitoneum and active pulmonary tuberculosis. Weight gain was maintained or continued after streptomycin had been discontinued, except in patients who relapsed or developed extraperitoneal tuberculosis.

Four patients had a *relapse* following initial improvement. One of these four died following the relapse and will be discussed in a separate case report. The three other patients were given a second course of streptomycin therapy to which two responded favorably while one remained unchanged. It is disputable whether or not two of these "relapses" represent true recurrences of peritoneal involvement. A patient with a history of pulmonary tuberculosis, considered inactive on admission, was treated with streptomycin, 2 gm. per day for thirty-three days, because of peritoneal tuberculosis. All abdominal symptoms and signs disappeared. Almost immediately after discontinuation of the antibiotic there was an upward trend of the temperature, weight loss and slight abdominal tenderness. At the same time a density in the left lower lung field was noted which increased slowly over a period of two months. Streptomycin therapy was resumed (1 gm. per day for seventy-nine days) and the patient responded again with subsidence of fever, weight gain and general improvement. Chest x-rays showed some clearing. The patient left the hospital against medical advice and further follow-up was not possible. It seems debatable whether this patient had a relapse of the peritonitis or a reactivation

of the pulmonary process, or both. The second patient who had responded remarkably to streptomycin, 2 gm. per day for seventy-four days, was discharged asymptomatic but returned five and a half months after completion of streptomycin therapy complaining of purulent discharge from the rectum. He was in good general condition, afebrile and had maintained his weight gain. A fistulous tract was found entering the rectosigmoid junction. The origin of this was not determined. This fistula must be considered a manifestation of tuberculosis but may be attributed either to peritoneal or intestinal involvement. The patient was given a second course of 216 gm. of streptomycin, under which therapy the fistula closed. The patient was asymptomatic six months after completion of the second course of streptomycin. The third patient had a definite relapse. His findings have already been described. He showed marked symptomatic and objective improvement on streptomycin therapy, the only remaining symptoms being occasional episodes of nausea, vomiting and/or mild diarrhea. Five months after cessation of therapy he again experienced abdominal cramps, watery diarrhea, increasing weakness and weight loss, and the lower abdomen was found to be markedly tender on palpation. X-ray studies revealed extensive involvement of the ileum and jejunum as well as the presence of a mass encroaching on the sigmoid and the cecum. The patient was given a second course of streptomycin (1 gm. per day for forty days). Abdominal symptoms remained unchanged and weight loss continued.

There were two *deaths* in the series; one case is described in Case 12. One patient with the complications of a draining sinus of the abdominal wall following paracentesis, a fecal fistula following laparotomy, active pulmonary tuberculosis and signs of mental disturbance failed to improve on streptomycin therapy. The sinus of the abdominal wall closed but no other improvement was noted. Streptomycin was discontinued after 72 gm. had been given in a seventy-two-day period because the patient had developed persistent nausea and had become increasingly disturbed mentally. He died twenty-one days after cessation of streptomycin therapy.

Follow-up observations have been possible in twenty-three of the twenty-six cases in this series. Three patients left the hospital against medical advice and could not be located. They had improved greatly under streptomycin therapy.

There were two deaths in the series. One patient died twenty-one days after a course of streptomycin to which he had not responded. One patient died six months after cessation of streptomycin therapy. He had shown good improvement but had a relapse a few weeks later. A second course of streptomycin was not given. Postmortem examination revealed extensive generalized tuberculosis with involvement of lungs, lymph glands, liver, spleen, adrenal and prostate.

The remaining twenty-one patients have now been under observation for varying periods of time. Two have been followed up for two to six months, two for ten months, five for thirteen to eighteen months, eight for nineteen to twenty-four months and four for twenty-six to twenty-nine months. At the last examination available the peritonitis was considered arrested or cured in twenty of these twenty-one patients. Fifteen of them had no symptoms or findings relative to the abdomen; five complained of minimal symptoms such as gas pains, constipation, occasional abdominal soreness or occasional slight pain. One patient who had never become entirely asymptomatic returned with an exacerbation of his illness five months after cessation of streptomycin treatment.

We are indebted to three patients of this series who agreed to a follow-up laparotomy shortly after completion of streptomycin therapy. (Table v, Fig. 3.) One of these cases is described in more detail in Case 6. In all three cases striking gross improvement had taken place between the two laparotomies. Free fluid was not present in the one patient in whom it had been found previously. The innumerable small nodules which had covered the parietal as well as the visceral peritoneum were no longer noted. Most impressive was the almost complete disappearance of the extensive ad-

TABLE V

LAPAROTOMY FINDINGS BEFORE AND AFTER STREPTOMYCIN THERAPY

Surgical and Pathologic Findings		Before Streptomycin			After Streptomycin		
		Case 24	19	6	1 mo. 24	6 wk. 19	1 mo. 6
Peritoneum	edematous	++					
	thickened	++				+	
Free fluid		++++					
Nodules	parietal peritoneum	++++	++++	++++	1 firm nodule		grossly ++calcified
	small intestines	++++	++++	++++	1 firm nodule	Few firm nodules	
	mesentery			++++			
	omentum					Few	
Adhesions	fine, fibrinous	++++	++++		++	+	+
	dense, fibrinous		++++	++++			
Matting of intestines				++++			
Intestinal obstruction			++				
Thickening of wall of pylorus			+++			++	
Thickening of stomach wall			+++				
Histologic Diagnosis	tuberculosis	+	+	+		+	+
	caseation		+	+		+	+
	acid-fast bacteria demonstrated		+				
New findings at 2nd laparotomy					fibrous plaques		
Duration of disease before Streptomycin		3 mo.	7 wk.	14 mo.			
Follow-up after completion of Streptomycin therapy					22 mo. Clinically well; part-time work	19 mo. Clinically well; working	21 mo. Clinically well; working

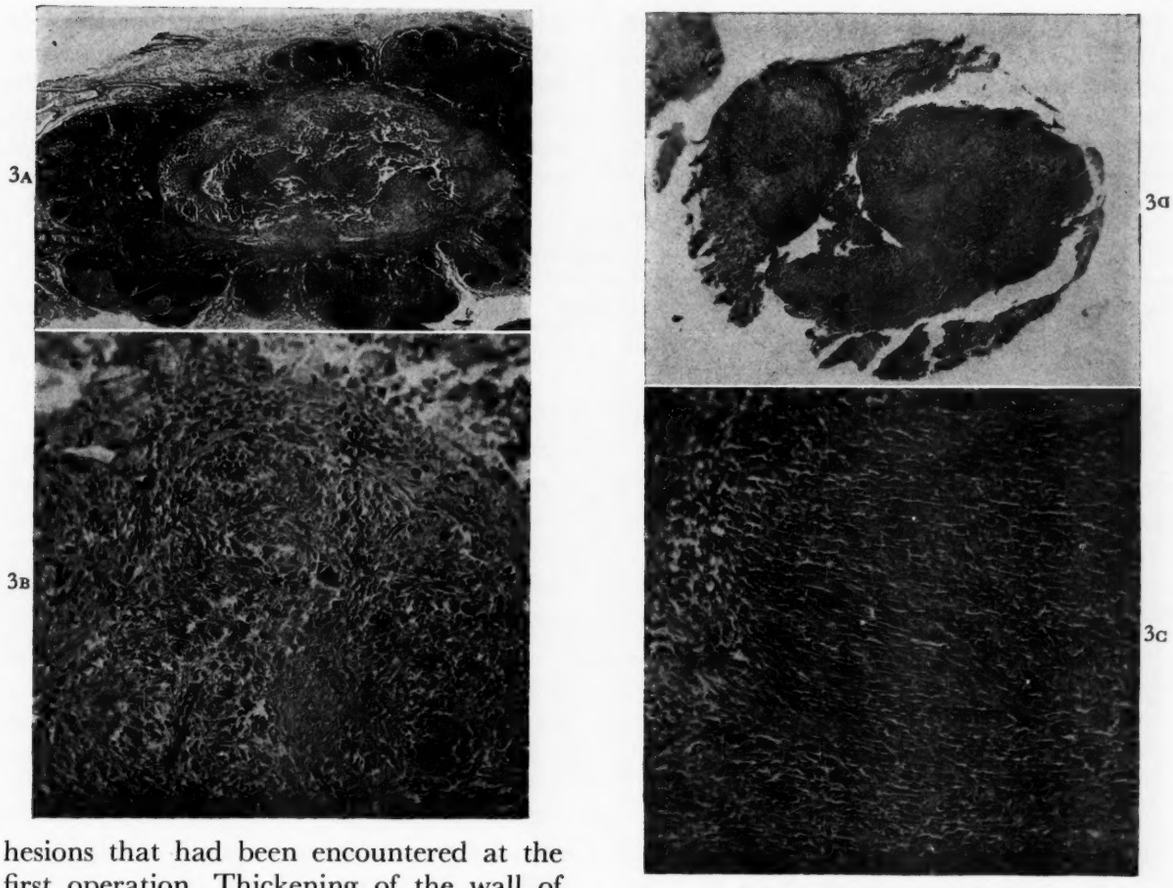

FIG. 3. Case 19. Lymph nodes. A, before Sm. × 20; B, before Sm. × 160; C, after Sm. × 30; D, after Sm. × 100; E, after Sm. × 400.

hesions that had been encountered at the first operation. Thickening of the wall of the stomach and pylorus found in one patient prior to streptomycin therapy had decreased notably. The remarkable gross improvement observed at the time of reinspection of the abdominal cavity was in keeping with the complete clinical recovery of the patients. However, there was histopathologic evidence of tuberculous activity in two of the three patients. In spite of the histopathologic findings all three patients have remained clinically well during follow-up periods of nineteen, twenty-one and twenty-two months, respectively; two of them have returned to full-time and one to part-time work.

While twenty-three of twenty-six patients recovered from the tuberculous peritonitis on streptomycin therapy, extraperitoneal tuberculosis was not controlled in eight of these twenty-three patients. (Table VI.) Three of these eight patients experienced reactivation of an old pulmonary process two, four and fourteen months after streptomycin had been discontinued. One of these patients was given a second course of streptomycin to which he responded; in one case the pulmonary tuberculosis was controlled by thoracoplasty and in the third no further follow-up has been available.

One case of apparently uncomplicated tuberculosis of the peritoneum seemed completely well twenty-one months after streptomycin had been discontinued. Physical examination, chest x-ray and study of gastric washings revealed no evidence of tuberculosis. Two months later he side of the peritoneal cavity. A shrunken, fibrotic gallbladder was removed. The histopathologic diagnosis was cholecystitis, chronic, apparently non-specific. There was no evidence of recurrence of tuberculous peritonitis. The patient was given a course of streptomycin for two weeks.

TABLE VI

RELATIONSHIP OF TOTAL DOSAGE OF STREPTOMYCIN AND RESPONSE TO THERAPY

Total gm. of Sm.		42	43	48	66	66	72	86	88	104	108	116	120	120	120	133	134	137	150	198	213	228	235	240	240	241	254
No. of Days of Treatment		21	43	29	66	33	72	43	88	74	60	60	120	120	120	74	67	137	95	107	120	120	120	120	120	121	127
Peritonitis	Improved	+	+	+	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
	Relapse	+	...	...	...	+	...	...	...	...	...	...	...	...	...	+	...	...	...	...	...	...	...	...	+	...	...
	Death	+	...	...	...	...	+	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Extraperitoneal Tb. before Sm.	Improved	..	+	...	...	...	...	..	?*	+	...	...	...	+	+	...	+	+	...	...	+	...	+	+	...	+	+
	Progressed	..	...	...	...	...	+	..	...	...	...	...	...	...	...	...	...	...	...	+**	...	...	...	...	...	...	...
Extraperitoneal Tb. developing	During Sm. therapy	..	...	...	...	...	...	...	...	...	...	...	...	...	+	...	...	+	...	...	+	...	...	...	...	...	...
	After Sm. therapy	..	...	...	...	+	...	+	...	...	+	+	...	...	...	...	...	...	...	...	+	...	...	...	...	...	...
No. of months of observation after completion of Sm. therapy		6	15	24	14	6	<1	27	0	24	29	26	2	10	14	28	22	18	0	21	24	19	0	15	10	20	21
Degree of rehabilitation		Home; not working; plans to go to school	Housework	Light work	Did not report for further follow-up	Home; school; rehospitalized after 2 yr.	Attending school	Attending school	Worked for 1 year; rehospitalized	Home; not working	Home; not working	Home; not working	Home; not working	Part-time work	Home; not working,	Home; not working	Hospitalized	Working	Rehabilitation center	Rehospitalized	Home; on limited activity,	Working						

* Pleural effusion had begun to decrease before Sm. therapy
** Progression of active pulmonary tuberculosis after discontinuation of Sm.

returned with active pulmonary tuberculosis. Mycobacterium tuberculosis was demonstrable in the sputum on smear, culture and guinea pig inoculation. Treatment with dihydrostreptomycin did not alter the disease process.

Another patient was well enough to enter school after about one year of convalescence although he had occasional attacks of cramping abdominal pain. Two years after cessation of streptomycin therapy he was readmitted with jaundice and pain in the right upper quadrant. A mass was palpable below the right costal margin. The clinical impression was that the patient had infectious hepatitis but because of persistence of the palpable mass a laparotomy was performed. The mass was found to be a tuberculous abscess of the abdominal wall out-

Pain in the right upper quadrant is still present but cannot be evaluated because of the recent surgery. Three of the eight patients developed new extraperitoneal tuberculous lesions while undergoing streptomycin therapy and while recovering satisfactorily from the peritoneal tuberculosis. In one of them peritonitis as well as adenitis with draining sinus improved but a minimal pulmonary infiltration, not present at initiation of treatment, became demonstrable. A second patient developed cervical adenitis while recovering from tuberculous peritonitis and pleural effusion and after streptomycin was discontinued a draining sinus developed in the biopsy scar. The last patient was showing marked improvement so far as tuberculous peritonitis, adenitis and minimal pulmonary

tuberculosis were concerned when a tuberculous abscess of the chest wall developed. This abscess was excised after completion of streptomycin therapy but recurred five months later. Seventeen months after streptomycin therapy a tuberculous lymphadenitis again developed and two months later bronchial secretions were found positive for Mycobacterium tuberculosis by guinea pig inoculation. It should be stated, however, that this patient was an alcoholic and did not limit his activities in spite of abnormal physical findings.

Duration of peritoneal involvement before initiation of streptomycin therapy had varied in the individual cases between two weeks and four to five years. The patients in whom the disease had existed for several years responded equally well as the patients who were treated soon after onset of the disease. (Fig. 4.)

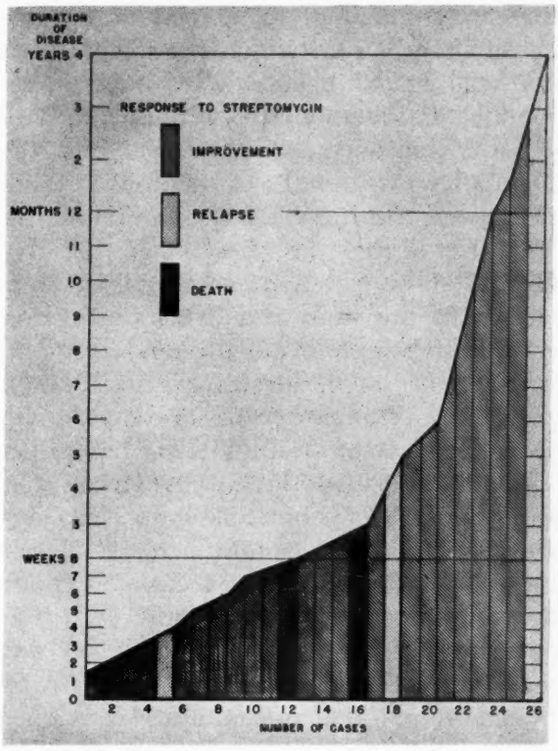

FIG. 4. Relationship between duration of disease and response to streptomycin therapy.

Dosage and Duration of Therapy. Patients who received 1 gm. of streptomycin daily improved as satisfactorily as those who were treated with larger daily doses. (Table VI.) No correlation could be demonstrated between total dosage of streptomycin administered, duration of therapy and the immediate or sustained result of such therapy. It will be noted that a relapse occurred in a patient who had received 240 gm. of streptomycin over a period of 120 days as well as in patients who had been given much smaller doses for a shorter time. In the first fatal case, in which the patient improved remarkably and then relapsed shortly after discontinuation of the drug, it would appear that continued therapy or a second course of streptomycin might have been beneficial. However, the second death, in a patient with coexisting pulmonary tuberculosis, was doubtless due to failure to respond to streptomycin rather than to inadequate medication.

Three patients in whom the diagnosis of tuberculous peritonitis had been made prior to admission were treated with streptomycin because of draining sinuses of the abdominal wall that had developed one, two and eighteen months after laparotomy. Other peritoneal symptoms were absent or negligible. The laparotomies had been performed three to four months after onset of the illness. In all three patients the surgical diagnosis was tuberculous peritonitis. This was confirmed by biopsy in all three, also by a positive guinea pig in one and by demonstration of acid-fast bacilli in the discharge from the sinus in another patient. All patients had fever and in one there had been considerable weight loss.

Streptomycin therapy was started one to four months after development of the sinuses. Defervescence and weight gain were observed in all three following initiation of streptomycin therapy. One of the sinuses that had developed one month before streptomycin treatment, while the patient was being treated with ultraviolet radiation, closed within two months. Therapy was continued for a total of five months (1 gm. per day for five days, 2 gm. per day for 145 days) and the sinus has remained closed for ten months (seven months after cessation of streptomycin therapy). One patient whose course was complicated by

the development of an abscess of the abdominal wall from which Proteus vulgaris and paracolon bacilli were isolated responded satisfactorily to streptomycin with general improvement and closing of the sinus after two months of therapy. Streptomycin was continued for two more months. The streptomycin dosage was 1 gm. per day for 122 days. Seven months after original closure of the sinus and five months after completed streptomycin therapy there was a recurrence of the draining sinus without recurrence of other peritoneal symptoms. A second course of streptomycin, 1 gm. per day for forty-two days, was given. The sinus closed again but follow-up is not yet available. In one patient a sinus of one month's duration did not close although general improvement was observed. The streptomycin dosage was 1.8 gm. per day for forty-two days. Three months after completed therapy a pneumonitis developed which responded clinically to penicillin. However, the temperature remained elevated. Because of fever and the persistence of acid-fast bacilli in the discharge from the sinus, the patient was given a second course of streptomycin; the dosage was 1 gm. per day for 108 days. No improvement was observed. Temperature elevation persisted and there was gradual loss of weight. The sinus continued to drain and after ten weeks on streptomycin acid-fast bacilli were still found in the drainage. The patient left the hospital while still on streptomycin and follow-up could not be obtained.

Toxicity. Toxic reactions to streptomycin were recognized soon after the introduction of streptomycin therapy. They have been widely discussed in the literature and have been analyzed in large series of patients.[1,59,60,74,75,76] The reactions encountered in this small series were in general similar to those encountered in any group of patients treated with comparable doses of streptomycin. This communication represents part of the study of the effect of streptomycin on tuberculosis conducted by the Streptomycin Committee of the Veterans Administration. A preliminary report on the cases of this series is included in the report of the committee.[1]

Although data on twenty-six patients treated with various regimens are of no statistical significance, it is of interest to note that in five of these patients streptomycin was discontinued because of apparent toxicity. These patients were treated approximately two years ago when our information on streptomycin toxicity was still quite limited. A review of these cases may be of value in view of our present knowledge.

TABLE VII

TOXIC MANIFESTATIONS OF STREPTOMYCIN ENCOUNTERED IN THE TREATMENT OF TUBERCULOUS PATIENTS*

Regimen gm	1.8–2.0	1.0	1.0	1.0–2.0
days	60–120	120	120	21–127
No. of daily injections	5	5	2	5–6
No. of patients treated	848	321	445	26

Toxicity	Incidence			
	%	%	%	%
Compelled cessation of therapy	8.5	5.0	2.0	19
Vertigo	76.5	34.3	23.1	38
Caloric stimulation, absent response	35.8	10.3	5.4	0
diminished response	28.6	23.9	25.2	15
Hearing diminution, voice	2.2	0.3	0.2	0
audiometer	15.2	4.0	9.5	?
Renal function, reduction	9.6	7.8	5.8	11
Albuminuria	23.2	17.1	11.0	4
Dermatitis, severe	3.7	1.2	1.1	0
mild	8.8	5.6	4.7	0
Eosinophilia, 6% or more	59.7	36.8	34.6	31
Fever	4.9	0.0	1.8	4
Blood dyscrasia	1.0	0.9	0.7	0

* The figures in columns 1, 2 and 3 are taken from Table 80.[74] Column 4 represents this series.

In one case streptomycin was discontinued because of local irritation at the sites of injection. The patient had received 133.0 gm. of streptomycin over a period of seventy-four days and had shown marked clinical improvement. Cessation of therapy could therefore be considered a safe procedure. The patient returned five months

later with purulent discharge from the rectum due to a fistula at the rectosigmoid junction. It is very questionable whether or not this could have been avoided by continued therapy. Local irritation after intramuscular injection of streptomycin is no more frequent than that observed following administration of aqueous penicillin. It usually has a short lived, benign course not followed by systemic reaction.[74]

In one patient a diminished response to caloric stimulation became demonstrable after only ten days of therapy (1.8 gm. per day) and after seventeen days the patient noticed headache, blurring of vision and vertigo. Streptomycin was decreased to 1.0 gm. per day on the twenty-second day of treatment and discontinued after twenty-nine days of therapy. The patient had shown excellent clinical improvement. She was kept on bedrest for three more months and ambulated gradually. She has remained clinically well for twenty-four months. Vertigo and blurring of vision cleared within approximately four months. Fourteen months later vestibular function tests and audiograms were interpreted as normal. The decrease in the daily dose of streptomycin did not affect the symptoms of vestibular damage which had developed already on the larger dose. The effect of the total daily dosage on the incidence of vestibular damage is now well recognized. Bunn and Westlake[74] report that the incidence of subjective vertigo with 1.0 gm. is 29 per cent and with doses of 1.8 and 2.0 gm. it is 76 per cent.

In one patient (Case 12) treated with 2.0 gm. of streptomycin daily the drug was discontinued after twenty-one days of therapy because of auditory symptoms, described by the patient as "a feeling like water in the ears." Audiometric studies were not available. The patient had had a good therapeutic response but relapsed promptly. An attempt of retreatment was carried out for only four days because of a recurrence of the auditory symptoms. The patient died four months later with generalized tuberculosis. With our present information regarding the therapeutic efficacy of smaller doses it would appear justifiable to continue streptomycin therapy in a similar case, keeping the dose at the minimum required and possibly combining it with the use of antihistaminics.[74–76]

The toxic symptoms in a case with peritoneal and pulmonary tuberculosis were difficult to interpret. The patient had shown psychotic tendencies during the entire hospitalization. After two months of therapy he complained of tinnitus and severe vertigo and also developed nausea and vomiting. Vestibular function tests could not be performed. Nausea and vomiting might have been due to toxicity but might also have been related to his uncontrolled disease. As he had shown at best only minimal response to streptomycin, discontinuation of antibiotic therapy after seventy-two days of treatment appeared indicated. The patient died twenty-one days later. Permission for autopsy could not be obtained.

In a fifth patient who had improved satisfactorily with defervescence, disappearance of ascites and of distention, the symptoms of anorexia, nausea, vomiting and abdominal cramps were probably related to the drug. They disappeared promptly when streptomycin was discontinued. Although nausea and vomiting are usually considered relatively minor toxic manifestations,[1] they are of importance in the debilitated patient in whom they also represent major symptoms of the basic disease. In cases of this type it seems advisable to discontinue streptomycin for a short time and to resume it if symptoms persist in the absence of specific therapy.

The number of patients in whom toxicity compelled cessation of specific therapy was relatively high in this series. It must be considered, however, that in several of these cases a satisfactory therapeutic response had been obtained and continuation of treatment did not appear justified in the presence of toxic symptoms.

The relatively low incidence of diminished response to caloric stimulation may be accounted for by the fact that vestibular

function tests were not performed in two of the patients who complained of vertigo. Interference of streptomycin with renal function was noted in three of our cases. There was a transient rise of the non-protein nitrogen to 46, 47 and 50, respectively. In two cases this subsided while the patients were still on streptomycin; in the third normal values were obtained six days after cessation of therapy. In one of these three patients the phenolsulfonphthalein excretion decreased from 95 to 47 per cent but returned to normal after streptomycin was discontinued. In one patient in whom retention of nitrogenous products and albuminuria were present before therapy there was no evidence of further damage, and under treatment the albuminuria as well as the non-protein nitrogen diminished. Transient albuminuria and occurrence of hyaline casts were observed in one case. It has been mentioned already that in one patient fever persisted during the entire course of therapy; the temperature became normal as soon as streptomycin was discontinued. The patient received penicillin simultaneously with streptomycin and, therefore, cannot be evaluated. Blood dyscrasia was not observed in this series. Leukocyte counts were low as a general rule in this group of patients. Two patients were given streptomycin in spite of initial leukocyte counts of 3,500 and 2,500. In the latter patient penicillin was added to the streptomycin therapy. In both patients there was a further decrease of the leukocyte count to 2,800 and 1,500, respectively. There was a reversion to pretreatment levels during continued streptomycin therapy. Neither of the patients developed granulocytopenia. One must assume that in these patients the leukopenia represented a manifestation of the disease and was not due to drug toxicity. It is interesting to note in this connection that these patients represent two of the three patients in whom new, extraperitoneal tuberculous manifestations developed during streptomycin therapy (cervical lymphadenopathy and tuberculous abscess of the chest wall).

COMMENT

It is well recognized that it is difficult to evaluate the effect of any type of therapy on tuberculous peritonitis. Diagnosis is sometimes difficult unless an exploratory operation is performed. Many cases are probably never recorded as cases of tuberculous peritonitis because the abdominal symptoms are overshadowed by other tuberculous manifestations or because there may be a striking discrepancy between symptoms, physical findings and the pathologic lesions found at laparotomy.[27] The frequently encountered impression that peritonitis is a relatively benign manifestation of tuberculosis is contradicted by the fact that in several large series[19,22,26] cures were effected in less than 30 per cent of the cases and the mortality has been as high as 55 per cent.[58,61] However, patients with tuberculous peritonitis may recover spontaneously and remain cured permanently. It is also significant that either a return of peritonitis or other tuberculous manifestations may develop in seemingly cured patients after years of freedom from any signs of active infection.[7,27]

It has been mentioned that medical supportive therapy has been combined with various medications, surgical procedures, different types of radiation and recently with antibiotic therapy. Surgical procedures as well as radiation therapy may be of value in selected groups of patients but the indications for their use have not been clearly defined. There has been general agreement that in patients presenting the picture of acute appendicitis, a ruptured viscus or intestinal obstruction surgical interference is definitely indicated. Konig[19] observed recovery in all forms of peritoneal tuberculosis following surgery. Others[8,61,62] have advised against laparotomy in the dry, plastic, adhesive or ulcerative types of involvement because of the danger of subsequent fistula formation. Rolleston[63] stated that operation is unnecessary in the fibrous and adhesive form and should be performed in the ascitic form only after medical treatment has been

given a fair trial, whereas according to Herman[61] the exudative form responds best to surgical procedure. The immediate postoperative mortality has varied between 3 per cent and 55 per cent.[19,58] Equally contradictory have been the indications for selection of cases for radiation therapy despite the emphasis in the literature that cases for heliotherapy and ultraviolet radiation must be carefully selected. Heliotherapy has been considered contraindicated in acute cases and in those in which there is pain, diarrhea or fever above 38.5°C.[28,48] The best results have been obtained in the adhesive form when the disease has been limited to the peritoneum. Brody[47] obtained his best results with heliotherapy in patients with fever. It would appear to us that the difficulties in the proper selection of cases for particular procedures would be further magnified by the rapidity with which changes from one type to another may take place. We have described the rapid changes from the ascitic to the adhesive type of involvement. The frequency with which both fluid and adhesions may be encountered simultaneously has also been noted. Finally and perhaps most important is the fact that the type and extent of involvement noted at laparotomy was not suspected on the basis of the preoperative physical examination.[27]

It was not necessary to consider the contraindications to certain forms of therapy previously discussed in the patients treated with streptomycin. This series does not represent a selected group of cases. All patients who were diagnosed as having tuberculous peritonitis were treated with streptomycin regardless of types or duration of the peritoneal involvement. The data in this paper demonstrate that fever, abdominal pain, diarrhea or pulmonary involvement are no contraindications to therapy, as they are not aggravated but ameliorated by streptomycin therapy. In addition, laparotomies could be performed with less hesitation because it could be anticipated that streptomycin would greatly reduce the danger of the development of postoperative draining sinuses, fecal fistulas and secondary infection. It is difficult to conclude from observations on only twenty-six patients that this can be accomplished. However, none of the patients developed any of these complications after streptomycin had been started, with the exception of one patient who developed a fistulous tract at the rectosigmoid junction five months after cessation of streptomycin therapy, eleven months after laparotomy. (Fig. 1, chart 3.) The other draining sinuses, fecal fistulas and secondary infections had developed before the patients were given streptomycin. In this particular group of patients, many of whom were treated at a time when streptomycin was not readily available, the antibiotic could not always be given immediately following the surgical procedure. It seems advisable however to start streptomycin therapy as early as possible after laparotomy because complications may develop within the first postoperative week. Preoperative use of streptomycin is probably unnecessary because of the rapid response to therapy and it is definitely contraindicated in laparotomies performed for diagnostic purposes. If the diagnosis can be established by other means, operation may be avoided. Good results have been reported following the intraperitoneal use of streptomycin.[54] This route of administration has not been used by any of the observers in this group. In one case of this series in which streptomycin ascitic fluid levels could be compared with streptomycin blood levels adequate diffusion of the antibiotic into the abdominal cavity had taken place.

A review of the cases presented in this report shows that in the majority of patients the response to streptomycin therapy was good. It is impossible to determine accurately whether or not the laparotomies performed in the majority of cases were major or contributing factors in the improvement of the patients. The effect of the laparotomies can be ruled out in five cases in which sixty or more days had elapsed between operation and institution

of streptomycin therapy. It may be ruled out tentatively in five other patients in whom the interval between surgical procedure and streptomycin therapy was fifteen to twenty-eight days and in whom improvement was noted only after streptomycin had been started. The question must also be raised whether a large percentage of this group might not have recovered without specific therapy. However, the response to streptomycin was so uniform, prompt and sometimes dramatic that it is justifiable to state that streptomycin shortened the disease process considerably in all patients who responded and in many cases unquestionably changed the trend of the disease.

Eleven of twenty-four patients who improved on streptomycin treatment had been ill for only two months or less and might have improved eventually on general supportive measures. In three of them, however, the illness was progressing rapidly prior to administration of streptomycin. Eight patients had been ill for three months to one year, the course of the disease being slowly but definitely downhill. Improvement was noticeable within one to four weeks. One patient had had four attacks of abdominal symptoms in the five months preceding treatment with streptomycin and there has been an asymptomatic period of two years following treatment. Four patients had experienced several acute episodes and spontaneous remissions for eight months to four years prior to streptomycin therapy. All four improved remarkably but one relapsed a few weeks after cessation of therapy. The other three have remained asymptomatic but they have not been followed-up long enough for proper evaluation. One patient while under observation experienced a remission with general supportive therapy only. This was followed by an acute episode which was treated with streptomycin. No difference was demonstrable between the spontaneous remission and that following administration of streptomycin. (Fig. 1, chart 7.)

Chronically ill patients responded as well as those with acute illness, and all types of peritoneal involvement encountered in this series were influenced by streptomycin clinically as well as anatomically. These findings represent a distinct difference from those noted in pulmonary tuberculosis in which " . . . the most satisfactory results have been observed in the exudative disease of short duration. Long standing pulmonary tuberculosis with cavitation and much fibrosis has not been appreciably benefited by the administration of streptomycin."[64] Several cases have been reported in the literature[6,19,27,30,62] in which extensive tuberculous peritonitis was demonstrated by laparotomy but years later at a second operation little or no evidence of tuberculous lesions or of adhesions could be found. In these cases there was no specific treatment. The disappearance of ascites, nodules and extensive adhesions observed in three follow-up laparotomies reported in this series was therefore not unprecedented but nevertheless impressive. As McDermott[64] has stated: "What we should anticipate from streptomycin and future antituberculous agents is not a dissolution of all tubercle bacilli within the body but rather the conversion of all, or nearly all cases, of certain types of active tuberculosis into the equivalent of the best results previously obtained by natural mechanisms." It is also of interest that the biopsy diagnosis in two of the follow-up laparotomies was tuberculosis in spite of demonstrable gross improvement and clinical recovery. It was not possible to decide whether these tubercles represented actual tuberculous lesions or non-specific granulomatous reactions. The previous findings in these patients leave little doubt that these residual lesions were tuberculous. Prolonged follow-up studies on these two patients will be particularly valuable.

Our results with streptomycin treatment of draining sinuses do not compare favorably with those of other observers.[53,65,66] Only one of three patients who had draining sinuses of the abdominal wall but no other peritoneal symptomatology improved satisfactorily; one patient responded but relapsed, and one failed to improve. In

all patients of this series in whom the draining sinuses complicated clinically active tuberculous peritonitis the response was good with the exception of one transient recurrence.

Three patients were retreated with streptomycin because of relapsing symptoms. Two of the patients responded favorably and one failed to respond. Sensitivity studies could not be obtained.

It was of interest to compare the response of various tuberculous manifestations in the same patient. No patient in whom extraperitoneal tuberculosis responded to streptomycin therapy failed to recover simultaneously from the peritonitis. Several patients, however, who recovered from the peritoneal involvement either did not recover from the extraperitoneal tuberculosis or developed new lesions elsewhere. Streptomycin has not prevented dissemination, and new tuberculous foci have occurred in cases in which simultaneous rapid healing of other lesions has been observed.[67] In the present series all forms of peritoneal tuberculosis responded to streptomycin therapy as well as or better than other tuberculous manifestations noted in the same patient.

" . . . It has been found possible to reduce the daily dose of 2.0 Gm. of streptomycin for 120 days to 1.0 gm. for the same period, with a decided reduction in toxicity and without detectable loss of therapeutic efficacy."[1] The information available from this study is not sufficiently extensive for final conclusions regarding the dosage and duration of treatment. The rapid response in cases of tuberculous peritonitis suggests that shorter courses of streptomycin may be sufficient to provide results equal to those obtained with prolonged treatment. It would appear that the administration of 1.0 gm. of streptomycin per day for forty-two days[1,69] would apply in most cases of uncomplicated tuberculous peritonitis. The anticipated incidence of drug-resistant strains of tubercle bacilli should be relatively low on a forty-two-day regimen.[69,70] Dosage schedules must, however, be adjusted to the individual patient and will depend to a certain extent on the presence or absence of extraperitoneal tuberculosis.

Any regimen should be followed, in our opinion, with a period of prolonged bedrest and close supervision of the patients after they have become ambulatory. Careful follow-up observations are an important consideration because of the frequency with which reactivation of peritoneal or extraperitoneal tuberculosis has been observed in this series regardless of the schedule employed. These observations emphasize that in tuberculous peritonitis, as in other forms of tuberculosis, the ultimate prognosis of the disease would be greatly improved if the development of streptomycin resistance could be prevented. Karlson et al.[71] have reported that the combined use of streptomycin, promin and para-amino salicylic acid may delay the emergence of streptomycin-resistant tubercle bacilli. Others[72] have concluded that the use of para-amino salicylic acid with streptomycin or dihydrostreptomycin seems to delay the appearance of tubercle bacilli resistant to these antibiotics and possibly improves the therapeutic results. Patients in whom highly resistant tubercle bacilli had developed under streptomycin therapy have been treated with para-amino salicylic acid. Following the administration of para-amino salicylic acid cultures of streptomycin-sensitive organisms could be isolated again from the same patients.[73] It would appear that while early results of streptomycin therapy of tuberculous peritonitis were good, the long term management of these patients might be greatly facilitated by the combined use of streptomycin or dihydrostreptomycin and para-amino salicylic acid. Relapses of tuberculous peritonitis should be retreated promptly and addition of para-amino salicylic acid to streptomycin should be considered. Further management of extraperitoneal tuberculosis should depend on the type of lesion encountered.

It may be concluded from the data presented that the majority of cases of tuberculous peritonitis respond favorably to streptomycin therapy. It has been noted

in the past that the immediate results following any type of therapy of tuberculous peritonitis have been more favorable than those observed in long term follow-up studies extending over a period of two years or more. Only seven of our patients have been under observation for two or more years. Continued follow-up studies will be necessary to determine whether the drug-induced remissions represent more than a temporary arrest of the disease.

SUMMARY

1. Twenty-six patients with tuberculous peritonitis were treated with streptomycin.

2. Twenty-five of the twenty-six patients responded favorably to streptomycin therapy. One patient with coexisting pulmonary tuberculosis failed to respond and died.

3. Four of the improved patients had a relapse. Two of them responded to a second course of streptomycin; one failed to respond. One patient was not retreated and died following a relapse.

4. A majority of the patients had been seriously ill and many were chronically ill. The uniformity and rapidity of response, the subsidence of fever and abdominal symptoms, the general improvement, the striking gross objective improvement observed in three follow-up laparotomies and the fact that six patients have returned to work are clear indications of the effect of the drug. In most instances streptomycin therapy changed the trend of the disease and shortened the disease process.

5. The duration and type of peritoneal involvement did not influence demonstrably the response to therapy.

6. Tuberculosis of the peritoneum responded as well as or better than coexisting tuberculous lesions elsewhere.

7. Streptomycin did not prevent the development of new lesions.

8. Comparable results were obtained with daily administration of 1 or 2 gm. of the antibiotic. The smallest amount of streptomycin needed for the arrest of the disease is yet to be determined.

9. Although immediate improvement following streptomycin therapy was excellent in most cases, continued observations will be necessary to determine the efficacy of streptomycin in the ultimate control of the disease. The development of new extraperitoneal lesions during and after therapy and the persistence of histologic evidence of tuberculosis in two cases make the prognosis extremely guarded.

Acknowledgment. We wish to express our thanks to the Staffs of the following Veterans Administration Hospitals and Centers whose cooperation has made this study possible: Chamblee, Ga.; Cleveland, O.; Columbia, S. C.; Dayton, O.; Excelsior Springs, Mo.; Hines, Ill.; Livermore, Calif.; Los Angeles, Calif.; Louisville, Ky.; Martinsburg, W. Va.; Memphis, Tenn.; Minneapolis, Minn.; Muskogee, Okla.; Oakland, Calif.; Oteen, N. C.; Rutland Heights, Mass.; San Fernando, Calif.; Springfield, Mo.; Staten Island, N.Y.; Wadsworth, Kan.; Walla Walla, Wash.; West Roxbury, Mass. and Wood, Wisc.

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Case reports will be included in the reprints.

Determination of C-reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever*

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In the absence of definite clinical indications the determination of activity of the disease process in rheumatic fever is often difficult. Many laboratory procedures have been used for this purpose in the past but none has been entirely satisfactory. Among those in most common use are the erythrocyte sedimentation rate, the total and differential leukocyte counts and the measurement of the P-R interval in the electrocardiogram. In recent years an attempt has been made in this laboratory to determine whether the presence of C-reactive protein in the serum is a useful indication of activity of the rheumatic state. Changes in the amount of C-reactive protein present were estimated only semiquantitatively. The appearance and disappearance of this protein and fluctuations in the amount present in the sera were correlated with clinical, hematologic and immunologic findings and the data thus derived form the basis of the present report.

C-reactive protein was first described by Tillett and Francis in 1930.[1] In the course of serologic studies using the somatic C polysaccharide of pneumococcus it was found that this substance reacted to form a precipitate when added to acute phase sera of patients with pneumococcal pneumonia but gave no reaction with sera obtained from the same patients during convalescence. This reaction was found not to be specific for pneumococcal pneumonia but was noted also in the sera of patients with acute rheumatic fever, staphylococcal osteomyelitis and subacute bacterial endocarditis. Later, Ash[2] demonstrated the occurrence of this reaction in sera of children with gram-negative bacillary infections caused by members of the colon-typhoid group. Later studies by Abernethy and Avery[3] on the properties of the reactive substance revealed that it was destroyed by heating above 65°C. and that it was associated with the albumin fraction of serum (0.5 to 0.75 ammonium sulfate saturation). It was pointed out that the substance was probably protein in nature. In addition, ionized calcium was found to be essential for the occurrence of the reaction. As a result plasma from oxalated or citrated blood would not react even though serum obtained at the same time reacted strongly.

MacLeod and Avery[4,5] devised a method for the isolation and purification of the C-reactive protein and produced in rabbits a specific antiserum against it which did not react with the proteins of normal human serum. The sensitivity of the tests for C-protein using the antiserum was greater than that using the C polysaccharide so that smaller amounts could be detected.

Löfström described a substance present in acute phase sera which caused nonspecific swelling of the capsules of certain strains of pneumococci.[6] As the result of a comparative study he concluded that this substance and the C-reactive protein were identical.[7] The investigations of Löfström[6] and Hedlund[8] have demonstrated that this protein is present in the blood of patients

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suffering from a wide variety of diseases. In 1947 McCarty reported the crystallization of this protein from the chest fluid of a patient with streptococcal empyema and from the ascitic fluid of a patient with cirrhosis and pneumonia.[9]

MATERIALS AND METHODS

Case Material. The rheumatic fever patients included in this study are from the wards of the Hospital of the Rockefeller Institute. They were admitted early in the course of the disease and were followed up well into convalescence. Serum samples, erythrocyte sedimentation rates, leukocyte counts and electrocardiograms were obtained at weekly intervals as a routine or more frequently if indicated. The serum was separated from the blood using sterile technic and was stored at 4°C. until used.

Antiserum. The antiserum was obtained by injecting into rabbits crystalline C-reactive protein of human origin.[9] The antiserum so produced did not react with normal human serum.

Test for C-reactive Protein. The precipitin tests were carried out in capillary tubes by a technic based on that described for the serologic typing of group A hemolytic streptococci.[10] A column of rabbit antiserum about 1.0 to 1.5 cm. long is drawn into the capillary (external diameter 1.7 to 1.0 mm.) and following this the tip of the capillary is dipped into the human serum to be tested and a similar volume drawn up. It is necessary to avoid the interposition of an air bubble between the two parts of the serum column. The column is allowed to run to the middle of the tube and the capillary is inserted upright in the plasticine of the pipette stand prepared as described by Swift, Wilson and Lancefield.[10] After incubation for two hours at 37°C. the tubes are placed in the refrigerator at 4°C. overnight before final reading. If no visible reaction occurs, the test is read as zero and a maximal precipitation which almost completely fills the capillary is read as +++++++. All gradations between the two extremes are encountered.

Antistreptolysin O. The method used for the determination of antistreptolysin O (ASO) was that described by Todd as modified by Hodge and Swift.[11]

Antistreptokinase. The antistreptokinase (ASK) titers were determined by the modification of Kaplan's method[12] described by Anderson, Kunkel and McCarty.[13]

Erythrocyte Sedimentation Rate. The erythrocyte sedimentation rate (E.S.R.) was determined by the Westergren method using oxalated blood.

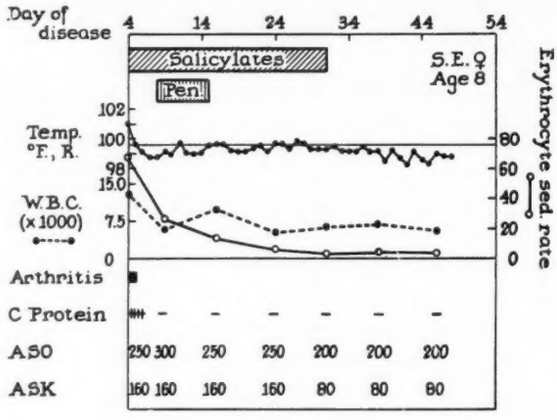

FIG. 1.

CLINICAL STUDIES

The correlation between the occurrence of C-reactive protein and other laboratory and clinical data is best presented by the description of representative cases. The following case reports selected from a group of forty-five illustrate the course of events in five patients with rheumatic fever of varying severity and clinical manifestations.

CASE REPORTS

CASE I. S. E. was an eight year old white girl who for three days prior to admission had pain, redness and swelling of her left knee, wrist, shoulder and ankle and a temperature as high as 103°F. Although there was no history of a preceding upper respiratory infection, group A, type 5 streptococci were isolated from her nasopharynx in small numbers. On physical examination the joints were found to be swollen and tender. In addition, there was a moderately long, loud, apical systolic murmur. Her temperature was 101°F. rectally, the total leukocyte count 13,100 and the erythrocyte sedimentation rate 67. There was a history of another attack of rheumatic fever two and a half years previously.

Her hospital course is illustrated in Figure 1. On salicylate therapy her temperature and E.S.R. fell rapidly to normal and the joint symptoms and signs disappeared. Penicillin was given orally to eradicate the streptococci present in the throat. The changing titers of the anti-

bodies suggest that she had had a recent streptococcal infection and that the organisms recovered from her nasopharynx did not merely reflect a carrier state. C-reactive protein was present in high concentration on admission but had disappeared from the serum four days later and never reappeared during the course of this illness. Her recovery was uneventful and she has done well since her discharge from the hospital.

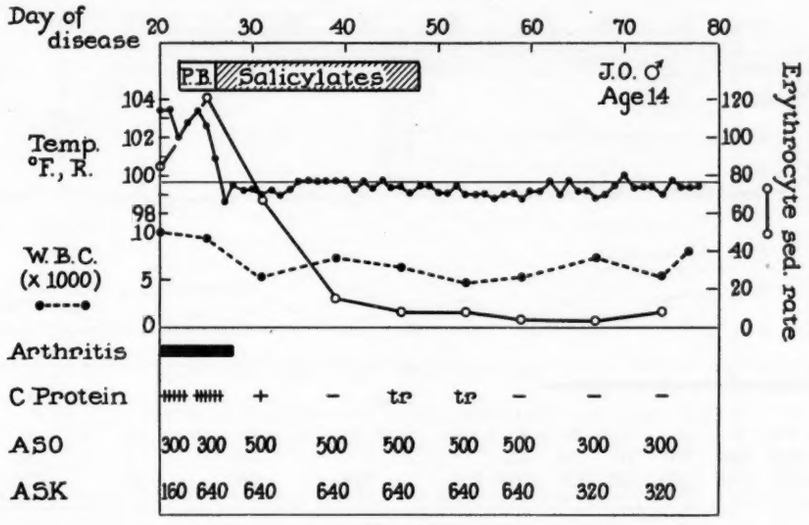

FIG. 2.

This case represents an unequivocal, yet simple, mild, "monocyclic" attack of rheumatic fever in a young child in whom convalescence was rapid and uncomplicated. C-reactive protein disappeared from her blood rapidly even before the erythrocyte sedimentation rate had returned to normal.

CASE II. J. O. was a fourteen year old white boy who became ill twenty days before admission with a severe sore throat and a temperature of 104°F. In three days his temperature returned to normal and he was able to return to school. Three days before admission he felt flushed, his temperature was found to be 102°F. and later that day there was pain in his left great toe. On the following day his left knee was involved and his physician noted a systolic murmur. He was admitted to this hospital on the following day. A younger brother had had rheumatic fever which resulted in mitral insufficiency and stenosis.

Physical examination on admission revealed the following significant findings, namely, the boy appeared acutely ill; his temperature was 103°F. rectally and his pulse rate 96. The throat was not injected. The heart was slightly enlarged to the left. The sounds were of fair quality. At the apex a moderately loud, blowing, systolic murmur was heard. In the third interspace just to the left of the sternum was a soft, blowing diastolic murmur. The left knee was painful on motion. There was definite heat, erythema and tenderness over the medial aspect of the metatarsal-phalangeal joint of the left great toe. The other joints appeared normal on examination. Hemolytic streptococci were not isolated from the nose or throat.

His hospital course is charted in Figure 2. In an attempt to assess the efficacy of antihistaminic therapy a total of 700 mg. of pyribenzamine® was administered over a period of four and a half days. Since little clinical response was noted, this was discontinued and salicylate therapy was instituted and continued for three and a half weeks. His temperature fell promptly to normal and remained there. The erythrocyte sedimentation rate which was 84 on admission rose to 121 on the fifteenth day, then fell rapidly and reached a normal value about three weeks after his admission. The arthritis disappeared after one day of salicylate therapy. The electrocardiogram on admission revealed a P-R interval of 0.22 seconds but all subsequent records were within normal limits. Significant increases were found in both streptococcal antibodies tested. There was a large amount of C-protein in the blood on admission and this persisted through the third week of his illness. As indicated in Figure 2 traces were present on two occasions later in the course of the disease.

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The exact significance of this is difficult to determine but when viewed in the light of the total experience with C-protein it appears most probable that this represented a period of low grade rheumatic activity. While this boy's course was slightly longer and more severe than that of the first patient, it was still essentially uncomplicated.

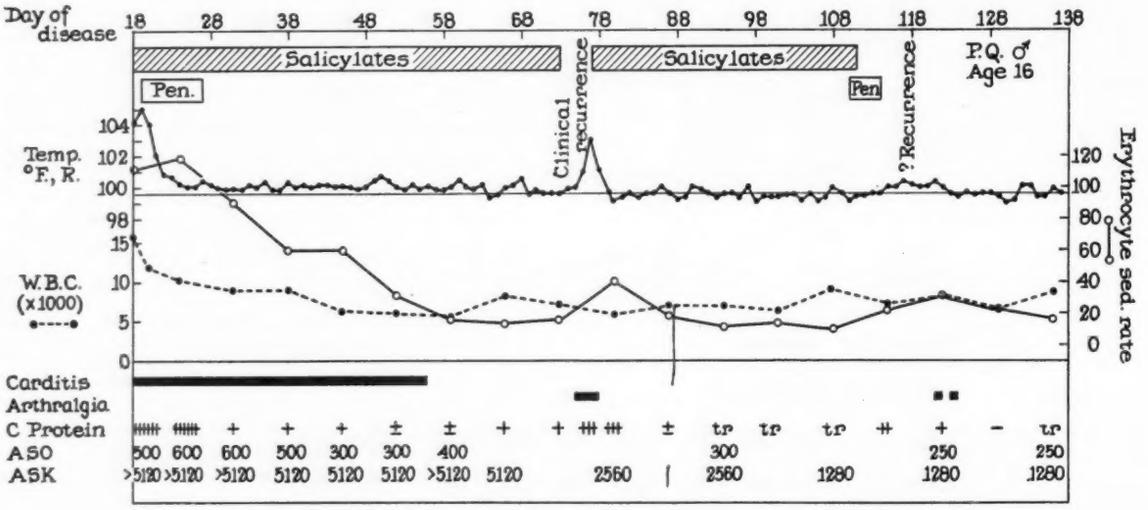

FIG. 3.

CASE III. P. Q., a sixteen year old white boy, gave a history of awakening with malaise and coryza eighteen days before admission. Later he had frank chills associated with a temperature of 102.5°F. and vomited three or four times. For three or four days he was markedly febrile without any specific localizing signs and following this a low grade fever persisted. Three days before admission his private physician made a diagnosis of recurrent rheumatic fever and started aspirin therapy. On the day of admission the physician noted that the patient's tachycardia had been replaced by a distinct bradycardia. A diagnosis of probable heart block was made and he was admitted to the hospital. A previous attack of rheumatic fever of four months' duration had occurred five years previously.

On admission the patient had a temperature of 104°F. rectally and appeared acutely ill. Auscultation of the heart revealed the typical murmur of aortic insufficiency. A marked arrhythmia was present and this was shown electrocardiographically to be a manifestation of second degree heart block (Wenckebach rhythm). Group A, type 5 streptococci were isolated from nose and throat cultures. His erythrocyte sedimentation rate was 112, the leukocyte count 16,000.

The subsequent course is illustrated in Figure 3. He was immediately placed on salicylate therapy and also on penicillin therapy as soon as the bacteriologic findings of the throat culture were available. The early course of the disease was stormy and for several days the patient had mild delirium. Electrocardiographic evidences of carditis persisted through the fifty-sixth day of his illness. The sedimentation rate gradually decreased and reached an approximately normal value in the ninth week of his illness. The white count soon returned to normal and he was relatively afebrile after one week in the hospital. The changes in the antistreptolysin 0 and antistreptokinase titers leave little doubt that he had had a recent streptococcal infection.

The test for C-protein was strongly positive on admission and for a week thereafter. It then decreased markedly but the protein did not entirely disappear from the blood except on one occasion on the 129th day of his illness. Salicylates were discontinued on the seventy-second day and the next day he complained of arthralgia. This was followed shortly by fever, an increase in the C-protein in the blood and later by an increase in the sedimentation rate. There was no increase in the white blood cell count. On the re-institution of salicylate therapy the fever and arthralgia disappeared and C-protein once more decreased in amount. On the 110th day penicillin was given prophylactically because of the occurrence of a streptococcal infection in another patient in the same ward. On

the 111th day salicylates were again discontinued. Several days later the amount of C-protein in the blood had increased, the sedimentation rate had risen and in a few days mild arthralgia appeared. Again there was no change in the leukocyte count. No salicylate was given and the abnormal findings disappeared spontaneously. The patient was sent home to complete his convalescence and has continued to do well.

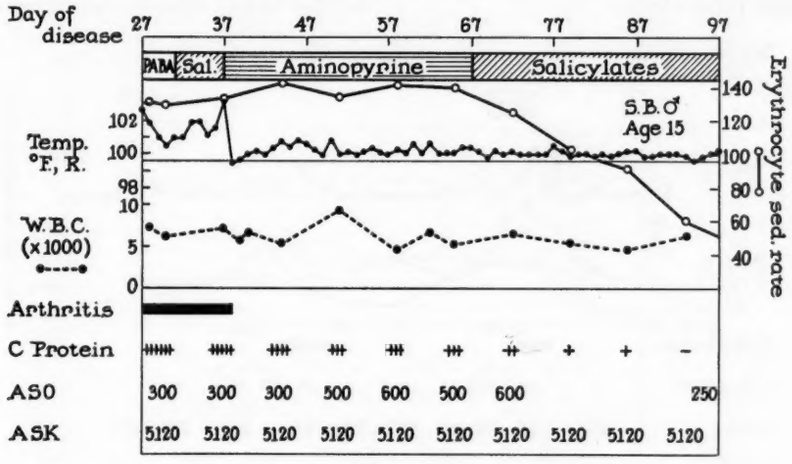

FIG. 4.

This represents a more severe and protracted form of acute rheumatic fever than the previous two patients. There was in this patient one clear-cut clinical recurrence of rheumatic activity and another probable recurrence. The changes in the C-reactive protein in the blood followed closely the clinical and laboratory signs of activity. Furthermore, the long-continued presence of C-protein, even though in small amounts, accurately depicted the smouldering character of the disease process when all other signs were absent.

CASE IV. S. B. was a fifteen year old white boy who had a very long illness characterized by many exacerbations and remissions. Four weeks before admission he became ill with a severe sore throat, high fever and swollen cervical nodes. He was treated for four days with one of the sulfonamide drugs, remained in bed for two more days and two days later returned to school. Nine days before admission malaise, fever, anorexia and pain in the right ankle developed. In the next three days his right knee, left ankle, hip and knee were successively involved. Two days before admission he noted severe substernal pain and a sense of pressure in the precordium. He was then brought to the hospital.

At the time of admission the posterior pharynx was injected but there was no exudate or purulent discharge. The heart was enlarged to the left; a gallop rhythm was present; there was a systolic murmur at the base and a precordial friction rub. The right knee and the left knee and wrist were swollen, painful and tender. The leukocyte count was normal, the erythrocyte sedimentation rate was 130 and examination of the urine revealed the presence of red cells, white cells, casts and albumin. Group A, type 30 streptococci were isolated from the nasopharynx. The P-R interval in his electrocardiogram was 0.24 seconds.

The first ten weeks of his hospital course are charted in Figure 4. He was first treated with para-aminobenzoic acid receiving 122 gm. over a four-day period. While the fever tended to decrease, there was no definite clinical improvement. The para-aminobenzoic acid was discontinued and aspirin was given in doses of 1 gm. every four hours. A serum salicylate level of 23 mg. per cent was attained on this dose. Because he remained febrile and the arthritis persisted, aminopyrine was substituted for the aspirin. Following this change in therapy the temperature returned almost to normal and the arthritis disappeared. On the forty-seventh day signs of heart failure appeared and the patient was digitalized. On the sixty-seventh day aminopyrine was discontinued and salicylates again given. The erythrocyte sedimentation rate remained extremely high during most of the period. (Fig. 5.) There was no decline noted until the seventh hospital week and it then fell gradually. The leukocyte count remained within normal limits and failed to mirror the clinical course of events. The P-R interval remained at

levels between 0.20 and 0.27 seconds for six weeks. There seems little doubt that the sore throat preceding his rheumatic fever had been streptococcal in origin. The antistreptolysin 0 titer rose significantly and the antistreptokinase titer, while constant, was one of the highest encountered in this laboratory.

charted. (Figs. 5 and 6.) At the time of his third recurrence (not shown) salicylates were given and were discontinued on the 298th day. (Fig. 5.) Nine days later the clinical syndrome previously detailed made its appearance followed two days later by fever; C-protein was present in the blood drawn the following day and in-

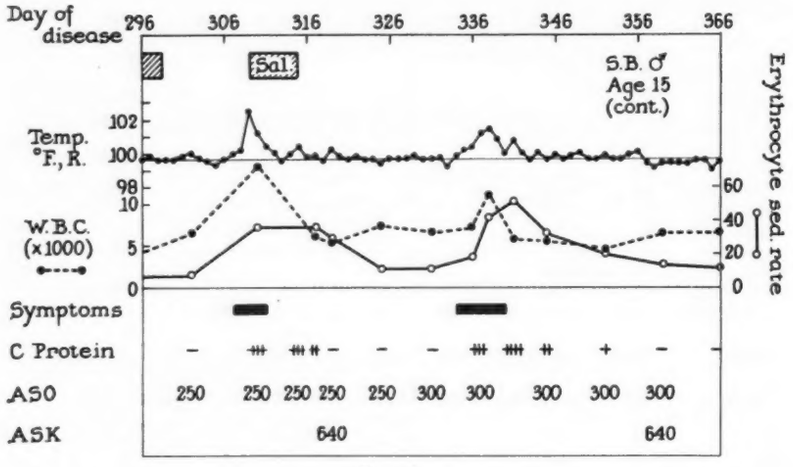

FIG. 5.

C-reactive protein was present in relatively large amounts on admission. There was a slow but definite decrease noted over a long period of time and finally on the ninety-third day it could no longer be detected. It was noteworthy that C-reactive protein had disappeared from the blood before the sedimentation rate had returned to normal. This finding was fairly consistent in a large number of cases which we observed.

For the next several months his hospital course was fairly satisfactory. The abnormal urinary findings gradually disappeared. There was some evidence of cardiac damage as indicated by the appearance of an aortic diastolic murmur during this period. On the 170th hospital day salicylates were discontinued and eleven days later he had the first of eight detectable recurrences of rheumatic activity. Each of these was ushered in by a remarkably constant sequence of events. He would first notice mild pain beneath one or both clavicles. This pain was not typically pleuritic or arthritic. No rub was heard at any time and x-ray examination consistently failed to reveal any abnormality to account for this pain. After the onset of the pain would come apprehension, anorexia and, on most occasions, fever.

The clinical and laboratory phenomena characterizing five of these recurrences are

creases in the erythrocyte sedimentation rate and leukocyte count were noted simultaneously. Salicylates were once again given; the symptoms and fever promptly disappeared; the white count returned quickly to normal; the C-protein left the blood and the sedimentation rate fell slowly to normal. There were no significant changes in the antibody titers during this period or later. It should be pointed out that although salicylates appear to be playing a role in controlling these exacerbations, the subsequent course of the patient showed quite clearly that the recurrences of activity were definitely self-limited regardless of whether salicylates were administered.

Similar recurrences were noted on the 334th, 375th, 406th and 431st hospital days. In the last three there was little or no febrile response; in two the leukocyte count never exceeded normal limits. C-protein was present in high concentration in the blood as soon as a sample was drawn after the onset of a clinical recurrence. It was the only consistent objective finding in all the recurrences. The boy was discharged from the hospital to his home in which he had additional episodes of a nature similar to those seen in the hospital.

In the case of this apprehensive individual who displayed numerous cycles of activity in which the symptoms were largely subjective in

character, the prompt and consistent appearance of C-protein in the blood was of considerable value in providing early objective evidence of disease activity. In the later and milder episodes this was the only positive finding accompanying the patient's rather vague complaints.

this regimen and by the time of her admission to the hospital two and a half weeks later her sedimentation rate, which had risen to a high of 115, was rapidly decreasing.

Physical examination at the time of admission was essentially negative. The leukocyte count

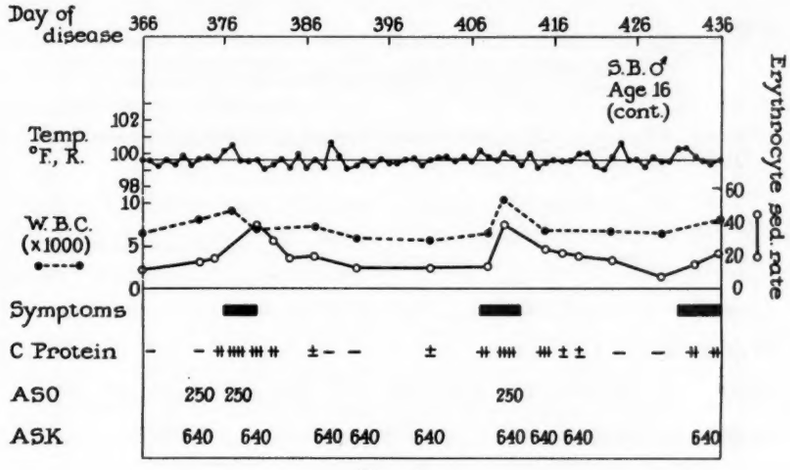

FIG 6.

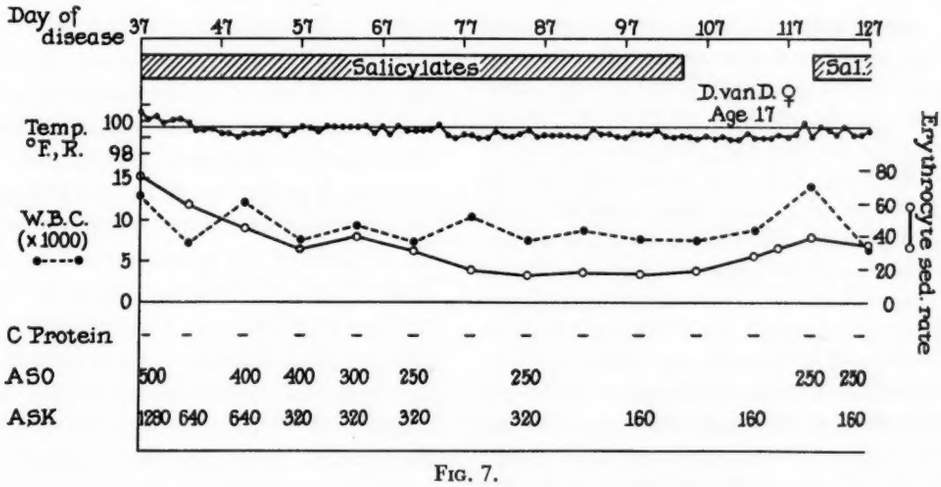

FIG. 7.

CASE V. D. van D. was a sixteen year old white girl who five weeks before admission was taken ill with a severe sore throat accompanied by a fever of 106°F. rectally. Her local physician made a clinical diagnosis of streptococcal sore throat and treated her with one of the sulfonamide drugs. She was kept in bed for one week after which she felt well enough to be up. One week later there was a recurrence of fever and she complained of pain in the right arm. The next day she had generalized aching in all her joints and her sedimentation rate was 100. She was put back to bed and given salicylate therapy. The symptoms were controlled under

was 13,050 with a normal differential and the sedimentation rate was 76 mm./hr. The electrocardiogram was normal, the P-R interval 0.18 seconds. An x-ray of the chest revealed no abnormalities. Most of her hospital stay is charted in Figures 7 and 8. She was asymptomatic and afebrile during this time. Her sedimentation rate fell slowly at first but never quite reached normal. It tended to stabilize between 20 and 30 mm./hr. Salicylate therapy was discontinued on the 104th day following which her sedimentation rate and leukocyte count rose and then fell again coincident with re-institution of salicylate therapy. On continuing therapy there was

another rise in the sedimentation rate and leukocyte count between the 147th and 160th day. During all this period C-protein was never present in her blood in detectable amounts and there was no fever, arthritis or carditis. She was discharged home but readmitted on two

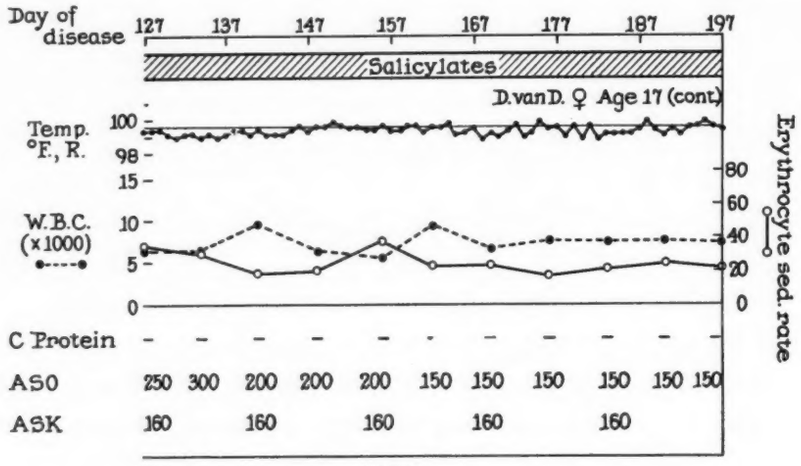

FIG. 8.

separate occasions later because of marked rises in her sedimentation rate. She was discharged from the hospital for the last time about eight months after the onset of her illness. Since that time she has been followed closely in our clinic for more than two years and she has done well. No evidences of heart disease have developed and there have been no frank recurrences of rheumatic activity but the sedimentation rate has on numerous occasions been higher than 30 mm./hr. In retrospect it would appear that the elevated sedimentation rate did not reflect rheumatic activity throughout the long period of convalescence and that the absence of C-reactive protein was a more reliable guide to the state of activity. Had the information that is now available concerning the implications of the C-protein test been at hand earlier, it is certain that the decision concerning the inactivity of the rheumatic process could have been reached more promptly. It would thus have been possible to avoid the long period of hospitalization and the attendant danger of psychologic invalidism.

REGULARITY OF THE OCCURRENCE OF C-REACTIVE PROTEIN IN RHEUMATIC FEVER

All of the forty-five patients studied in this series had moderate to large amounts of C-protein (+++ to ++++++) in the blood during the acute attack, with the exception of the fifth patient who was probably well on the road to recovery from a simple, monocyclic attack of rheumatic fever at the time of admission. The occurrence of the protein was observed with almost as great regularity by Rothbard et al.[14] even though the somewhat less sensitive test procedure using pneumococcal C polysaccharide was employed.

Tests for C-protein have been carried out on the sera of ninety patients observed in an epidemic of scarlet fever at the Great Lakes Naval Training Station. Data on the antistreptokinase, antistreptolysin 0, antidesoxyribonuclease and gamma globulin content of these sera have been published.[13,15] While sera were available only at weekly intervals and a precise correlation between the occurrence of C-protein and the activity of the rheumatic state has not been attempted in these cases, certain facts of interest appear in comparing the results obtained in patients in whom rheumatic fever developed following scarlet fever and those in whom it did not. Of sixty-seven scarlet fever patients studied who were considered as showing no evidence of rheumatic fever, forty-nine had C-protein in the blood only at the time of the scarlet fever and it disappeared rapidly during convalescence and remained absent. For the most part, those patients who showed per-

sistence or reappearance of C-protein had an adequate explanation in the form of a cross infection with another type of streptococcus or of some complicating disease. The importance of cross infection is emphasized by the fact that of the forty-one patients of this group from whom only a single type of streptococcus was isolated all but two showed prompt and permanent disappearance of C-protein following the attack of scarlet fever while sixteen of the eighteen cases in which there was direct cultural evidence of cross infection were among those showing abnormal C-protein patterns. These data may be compared with those obtained from the twenty-three patients in whom rheumatic fever developed as a sequela of scarlet fever. Of this group twenty-one showed either persistence of C-protein for two to six weeks after the scarlet fever or a second appearance at the time of the onset of rheumatic fever. Thus in the cases in which it was possible to follow the development of the disease from the time of onset of the streptococcal infection, the occurrence of C-protein reflected the appearance of a complicating disease process.

The C-protein data of these rheumatic fever cases are of interest in connection with the discussion concerning the nature of the so-called "latent period" in the disease. The question arises whether this period between the streptococcal infection and the onset of frank manifestations of rheumatic fever is actually free of disease activity or merely represents a period of low grade activity during which objective manifestations are at a minimum. Insofar as the test for C-protein can be relied on as an extremely sensitive indication of disease activity, these data would indicate that in some cases the latent interval is actually a quiescent period since in several instances C-protein was entirely absent in the period between the recovery from scarlet fever and the onset of rheumatic fever.

COMMENTS

The results of the study on the occurrence of C-reactive protein in patients with acute rheumatic fever suggest that its presence in the blood is a sensitive, and perhaps the most sensitive, indication of activity of the disease process. In the few cases discussed in detail in this paper and in many others observed in this hospital, it has been in our experience the most consistently positive laboratory test in the presence of rheumatic activity. The changes in the amount of C-protein present tend roughly to parallel changes in the erythrocyte sedimentation rate but this is by no means invariably true since C-reactive protein may be absent from the blood when the sedimentation rate is much higher than normal. In fact, in the early recovery period in rheumatic fever the C-protein reaction usually becomes negative before the sedimentation rate has returned to normal. This is not an invariable relationship, however, and C-protein may be present in the blood when the sedimentation rate is normal. This discrepancy probably indicates that C-reactive protein is not in any important way related to or responsible for changes in sedimentation velocity although this point has not been conclusively tested experimentally. The leukocyte count, in our experience, has not been an accurate guide to the presence of rheumatic activity.

It should be emphasized that the test for C-reactive protein is usually of little help in the differential diagnosis of rheumatic fever since other diseases with closely related clinical pictures such as rheumatoid arthritis and subacute bacterial endocarditis also are characterized by the presence of C-reactive protein. Once the diagnosis of rheumatic fever has been made, however, the test is of real value. Its practical value is illustrated by the following case. A young boy convalescing uneventfully from acute rheumatic fever was about to be discharged from the hospital when right lower quadrant pain, tenderness and a low grade fever suddenly developed. The obvious diagnostic problem was that of differentiating between acute appendicitis and a recurrence of rheumatic fever. C-protein had been absent from the blood for some time and on the

basis of previous experience with the test it was reasoned that in the presence of rheumatic activity accompanied by these clinical manifestations C-protein should have made its reappearance. The test was carried out and no evidence of precipitation occurred after two-hour incubation at 37°C. The boy was subjected to a laparotomy and an acutely inflamed appendix was removed. With appendicitis of longer standing C-protein would probably have appeared but early in the disease it was absent.

It is evident that the procedure described here for the estimation of C-reactive protein is not one that can be widely used as a clinical laboratory test in rheumatic fever. The difficulties involved in obtaining appropriate material and in the isolation of C-protein of sufficient purity to be used in the preparation of rabbit antiserum sharply limit the availability of the test reagents. However, the earlier procedure in which is used a solution of pneumococcal C polysaccharide, a substance which can be readily prepared from pneumococcal cells, possesses a similar usefulness. It differs primarily in its sensitivity so that a somewhat larger amount of C-protein must be present in the blood before positive results are obtained.

With the necessary reagents at hand the antiserum test is a simple one requiring only minute amounts of the patient's serum and of the rabbit antiserum. A number of tests can be set up very quickly and no difficulty is encountered in reading the results. Since C-protein is not present even in trace amounts in the sera of normal, healthy individuals, positive results provide unequivocal evidence of the activity of some pathologic process. The poorly defined "normal range" of the sedimentation rate has been the basis for uncertainty in the evaluation of activity of rheumatic fever in several cases in this hospital as illustrated by Case v and the C-protein test has proved to be of value in resolving these difficulties.

It is interesting to note that in several patients with classic Sydenham's chorea, a disease which is generally conceded to be a manifestation of rheumatic fever, C-reactive protein has not been present in the blood. No explanation for this will be attempted here.

SUMMARY AND CONCLUSIONS

The use of the presence of C-reactive protein in the blood as a measure of the activity of the disease process in acute rheumatic fever is described. The clinical charts of a number of patients illustrating its use are presented.

The available evidence seems to indicate that the presence of C-reactive protein is probably the most sensitive test for the presence of rheumatic activity that we now possess.

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Zoster-like Eruptions Caused by the Virus of Herpes Simplex*

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HERPES zoster as it is at present understood seems to be principally a disease of the posterior root ganglia and their cranial nerve analogs, to which epithelial lesions are secondary.[1] Classically, the epithelial lesions assume a segmental distribution corresponding to the sensory nerves emanating from one or more ganglia. Herpes simplex, on the other hand, is primarily a disease of the skin and mucous membranes which does not customarily produce segmental lesions and in which infection of the nervous system, as far as existing knowledge goes, appears to be altogether infrequent. Zoster is not given to recurrence, in striking contrast to simplex in which recurrence, not rarely repeated over the course of many years, is very common. Although the clinical differences between zoster and simplex are often unmistakable, they are not always so. Not only may the two diseases mimic each other but also several writers have recognized a borderland in which they merge and have described cases in which it is impossible to say on clinical grounds alone whether the disease is herpes zoster or herpes simplex.[2,3]

In the light of knowledge accumulated during the past thirty years the etiologic agents of zoster and simplex have emerged as distinct viruses.† The distinction rests chiefly on differences in the over-all pattern of disease they usually produce in the human host and in transmissibility to common laboratory animals. The virus of zoster may have been artificially transmitted to humans[4] and has been propagated in human skin grafted upon the chorio-allantois of hens' eggs[5] but, with the exception of a few contradictory reports to be considered later in detail, it has not been successfully transmitted to any of the animals commonly employed in the laboratory.[6,7] On the other hand, the virus of simplex may be rather readily transmitted to rabbits, to a variety of rodents and to chick embryos.[8] The agents that cause the two diseases also have certain properties in common. Each as it exists in nature is exclusively a parasite of man. There is no essential difference in the evolution, the gross appearance or the histopathology of the basic lesion that each evokes in the skin and mucous membranes. Acidophilic, intranuclear inclusion bodies (Cowdry's "Type A") in certain of the host cells at particular stages of the development of the lesion are common to both.[9] Thus it seems likely that these agents may stem from a common ancestor.

Despite their differences it is therefore not surprising that herpes zoster and herpes simplex have been confused on both clinical and etiologic grounds. It is probable that the claims already alluded to, to have transmitted zoster to rabbits, are based upon cases in which the infecting agent was actually simplex virus. Some authors have recognized this to be the case. It is the purpose of the present report to set down several

† There is as yet no valid basis other than anatomic distribution of lesions and certain epidemiologic considerations for separating herpes genitalis and herpes simplex. For the purposes of the present discussion the two will be considered to be caused by the same agent, namely, the virus of herpes simplex.

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cases of zoster-like disease caused by the virus of herpes simplex. On the basis of these and of similar cases previously reported by others it is hoped to be possible to point out certain clinical differences that may aid in suggesting an etiologic diagnosis. In presenting our own cases and in reviewing those culled from the literature we have arranged them in three categories: (1) those with an herpetic eruption of some part of the sensory trigeminal field, (2) those of the trunk and extremities and (3) those of the fingers. The reasons for this arrangement will become apparent as the subject is developed. Needless to say, only those cases from the literature will be considered in which there is some reason to think that transmission of simplex virus to animals from the lesion in question may have been accomplished. Many attempts that yielded negative results can be found[6,7] and will not be considered here.

Before proceeding with a review of the literature it will be useful to examine what constitutes reasonable evidence of the transmission of simplex virus from man to animals as well as the probable relationship of virus so transmitted to disease in a patient.

The more or less time-honored method of accomplishing the transfer of the infection from the original human source to a laboratory animal is by inoculation of suitable material upon the scarified cornae of a rabbit.* Simplex virus produces keratoconjunctivitis in the animal and sections of the cornea if taken before necrosis is too far advanced (as a rule, from twenty-four to seventy-two hours after inoculation depending on the strain of the virus) will show the intranuclear inclusion bodies principally in epithelial cells. The inclusion bodies are most numerous along the lines of scarification. Some strains of the virus produce only localized keratoconjunctivitis when first transferred to the cornea of the rabbit. With other strains the virus, progressing along axons of the trigeminal nerve from the cornea to the pons, is capable, even on first transfer, of causing in the animal clinically evident and frequently fatal encephalomyelitis.* Providing that the course of the infection of the nervous system is not protracted or that the animal is killed after a few days, inclusion bodies are readily identifiable in nerve cells and glial cells in suitable sections of the brain. Using pus from the conjunctival sac the virus may be propagated either by corneal inoculation of additional rabbits, by intracerebral inoculation of an animal such as the mouse or by inoculation of egg membranes. Infective brain substance may also be used for propagation.

Within the limits of the foregoing facts the following statements might be regarded as adequately summarizing "reasonable evidence" of the transfer of simplex virus to animals: (1) the production, by direct inoculation from the human source of keratoconjunctivitis in rabbits, of encephalomyelitis in mice or of "plaques" on the chorio-allantois of eggs together with the demonstration of inclusion bodies of the herpetic type in the appropriate tissue of the animal concerned; (2) the production in the rabbit of keratoconjunctivitis followed usually with one or two weeks by signs of encephalomyelitis. Although this sequence of events is in itself highly suggestive, inclusion bodies should be demonstrated in the brain.

It must be admitted that such evidence as the foregoing is incomplete. However, it does signify with a high degree of probability that one is dealing with simplex virus. It reduces considerably but does not eliminate the possibility that one may be dealing with a human pathogen other than the virus of herpes simplex or with an agent of an enzootic of the animal chosen for inocu-

* Transfer from human tissues may also be achieved by inoculating vesicular contents or other material either upon the chorio-allantois of fertile hens' eggs or intracerebrally in mice or other susceptible animals.

* The phenomenon of axonal transmission of simplex virus from the periphery of the body to the central nervous system or to ganglia outside it has not been proved to occur in man. It has, however, been conclusively demonstrated in the rabbit,[10] in the mouse[11] and in the chick embryo.[12]

lation. Immunologic demonstration of the similarity of the agent to simplex virus provides an important and final link in the chain of evidence. It may consist of neutralization or complement-fixation tests using the suspected agent and a serum prepared against a known strain of the virus or it may take the form of cross-protection tests in animals.

Whether herpes simplex virus transferred from a lesion of man to animals is actually the cause of the human lesion may be considered by some to be a more contentious matter. Once infection of man with simplex virus occurs there is reason to believe that the virus remains indefinitely in the tissues giving rise to a high titer of specific antibodies that endures for very many years, perhaps for life.[13] Fully three-fourths or more of the adult population possess such antibodies.[8,13]

It might be held, then, that the recovery of the virus from certain infectious lesions of human tissues is adventitious, that its presence is only a manifestation of its latency (or, at best, that it is aroused to activity by another and primary agent) and, therefore, that it has no essential relationship to the lesion at hand. Such an argument would be more disturbing if the virus had been shown even occasionally to be present in non-herpetic lesions. There do exist, it is true, a few reports of the isolation of simplex virus from saliva in the apparent absence of herpetic lesions of the mouth[14–16] and two reports of its presence in the cerebrospinal fluid in the absence of clinical evidence of disease caused by it in the meninges or the nervous system.[17,18]

Without belaboring the argument it seems obvious that these rare demonstrations are by no means testimonials of the ubiquity of the virus in human tissues or even of its latency, in a restricted sense of the word. Comparatively trivial and undetected disease seems its more likely source. In circumstances in which simplex virus is isolated from diseased human tissues it is the opinion of the present authors that very little doubt of the etiologic relationship of the virus to the human lesion can obtain if the basic lesion is of a type known to be caused by the virus. If, in addition, typical inclusion bodies are seen in the human tissue, the evidence may be regarded as complete.

The specific antibody response of patients is of aid in resolving doubt only when the herpetic infection is of the primary type for it is only in cases of this type that it is possible to show the absence of specific antibodies at the onset of the disease and their appearance during convalescence—proof of the causative relation of the virus isolated from a lesion to the disease in a patient. In patients in whom disease is due to a recurrence of the activity of simplex virus the presence of antibodies at the onset of the recurrence is to be expected.

REVIEW OF THE LITERATURE

Zosteriform Eruptions of the Trigeminal Area. The first report of the isolation of simplex virus from a zoster-like eruption of the face was that of Teague and Goodpasture.[2] Their patient, a male of forty-five years, presented a cluster of vesicles in a linear area on the skin directly over the course of the right supra-orbital nerve. The lesion was accompanied with pain in the right side of the head. The authors state that clinically the disease was typical neither of zoster nor simplex. Fluid from the vesicles produced keratitis in rabbits and inclusion bodies were seen in the corneal epithelium of the animals.

Freund[3] described two cases somewhat similar to that of Teague and Goodpasture. In both of them the eruption was over the area of the skin supplied by the second branch of a trigeminal nerve but in neither was the whole of the area involved. In one case the eruption was known to have been recurrent. It was not painful in either. Vesicular fluid from the first case evoked keratoconjunctivitis, but not encephalitis, in four rabbits; one of the animals was subsequently shown to be immune to an intracerebral injection of a known strain of simplex virus. Material from the eruption

of the second case also produced keratoconjunctivitis in rabbits; inclusion bodies were demonstrated in the cornea of one of the animals.

Zosteriform Eruptions of the Trunk and Extremities. In his original studies of herpes zoster Lipshütz[9] described attempts to transmit an infectious agent from several cases to the cornea of rabbits. Most of the attempts are to be regarded as unsuccessful. Two cases deserve mention here. The first (Case I) is described as zoster of the thorax of three days' duration. Vesicular fluid was inoculated upon the scarified cornea of a rabbit; four days later opacities were noted along the lines of scarification. Occasional inclusion bodies of the herpetic type were found in epithelial and connective tissue cells of the cornea. The other case (Case IV) was one with a very early eruption of the chest. Material from the lesions produced keratoconjunctivitis in a rabbit. An exceptionally large number of inclusion bodies was seen in the corneal epithelium. No further studies of either case are reported.

Marinesco and Draganesco[19,20] studied three cases of zoster. Attempts to transmit an infectious agent from two of them were unsuccessful. The third, a boy of eighteen years, had a vesiculopustular eruption over the left flank. The eruption was accompanied with pain. It is of interest that the cerebrospinal fluid showed lymphocytic pleocytosis. Of three rabbits inoculated upon the cornea with fluid from the vesicles, two developed keratoconjunctivitis. The cornea of one of them was examined microscopically and was found to contain inclusion bodies of the herpetic type. The authors believed that they had transmitted zoster virus to rabbits.

Milian's patient,[21] a male of thirty-eight years, had recurrent herpes of the left buttock. The initial eruption was diagnosed as herpes zoster. The lesions were never painful; they healed with scar formation. Material from the vesicles of a recurrence produced keratoconjunctivitis in a rabbit, followed a week later by clinical evidence of encephalitis. The agent was also encephalitogenic when inoculated subdurally in rabbits. No histopathologic or immunologic studies were carried out.

Luger and Lauda reported two cases. The first[22] was that of a male of forty-five with a painful eruption over the right gluteal region. Fluid from the vesicles produced keratoconjunctivitis and encephalitis in rabbits. The infection was transmitted serially and herpetic inclusion bodies were seen in both the cornea and the brain of some of the animals. A rabbit that survived was subsequently shown to be immune to a known strain of simplex virus. The second case[23] was that of a male of forty-three. The eruption was over the left side of the back at the level of the fifth dorsal vertebra and extended into the left axilla and over a portion of the left upper arm. It was accompanied with intense neuralgic pain. The axillary lymph nodes on the affected side were enlarged and tender. The infection was transmitted to rabbits in series. Histopathologic and immunologic studies similar to those of the first case established the infective agent as simplex virus. It is worthy of comment that the original inoculation of this strain on the cornea of a rabbit resulted in the death of the animal from encephalitis eleven days later despite the fact that no signs of keratitis were noted. Subsequent inoculation of the agent after it had undergone several brain-to-brain passages resulted in keratoconjunctivitis. The present authors have witnessed a similar course of events with two strains of what was ultimately proved to be herpes simplex virus. The true state of affairs seems to be not that the virus fails initially to produce keratitis but rather that the reaction of the cornea and conjunctiva is so slight that it is overlooked.

The case reported by Pincherle and Vegni[24] was that of a young male convalescent from lobar pneumonia. The patient developed herpes labialis and, eleven days later, an herpetic eruption over the right buttock. The onset of the latter was accompanied with slight, stinging pain. Vesicular fluid from the zosteriform lesion

on the buttock caused keratoconjunctivitis and encephalitis in rabbits and was transferred to rabbits in series. Two animals that had survived corneal infection with material from a case of herpes labialis were immune to corneal inoculation with the strain from the patient. No histopathologic observations were reported.

Although the evidence that simplex virus was isolated from a zosteriform lesion of a case described by Minami and Ehara[25] is incomplete, the case is included because its clinical aspects enhance the likelihood that simplex virus may actually have been the cause. The patient, I. E., a twenty-six year old male, was subject to recurrent herpes of the penis. On one occasion associated with a recurrence of the genital lesion about ten painless vesicles appeared on the outer surface on the left thigh followed ten days later by a crop of vesicles on the outer side of the right upper arm. Both episodes were thought to be zoster. Two days after the appearance of the lesion of the thigh contents of the vesicles were transferred to the cornea of one rabbit and the testicle of another, with positive results in both instances. However, no mention is made of inclusion bodies and no immunologic studies were done. The significance of the positive results obtained by the inoculation of rabbits with vesicular fluid is clouded by a claim also to have produced herpetic orchitis in a rabbit by inoculation with the patient's blood—a highly improbable circumstance.

Freund[3] mentioned but did not describe the case of a male patient who suffered from recurring zoster-like eruptions of the buttocks. He stated that he was able to isolate a highly virulent strain of simplex virus from the vesicles but he did not give the evidence upon which the claim was based.

The case of Ota and Miura[26] was that of a female of forty-eight who for three years had experienced recurrent zosteriform eruptions of the left arm. The recurrent nature of the disease makes it seem probable that it was due to simplex virus. However, the evidence does not permit an unqualified conclusion in this respect. In the first place the authors employed testicular inoculation of rabbits in their efforts to transmit the infection. Although one may achieve a "take" with simplex virus by this means, the testicular route of inoculation in rabbits enhances the possibility of confusing simplex with Virus III, the cause of an enzootic of these animals that forms inclusion bodies similar to those of herpes.[27] Moreover, although a rabbit inoculated in the anterior chamber of the eye with the testis-passaged agent developed paresis of the hind legs, the neurologic disturbance was much more likely coincidental than due to simplex virus for it appeared twenty-four hours after the ocular inoculation. The authors make no mention of inclusion bodies and did no immunologic studies to identify the agent. They believed that they had succeeded in transmitting zoster to rabbits. Three other cases of zoster that they studied, presumably using the same technic, gave negative results.

Beeuwkes' patient[28] had recurring herpes labialis. The zosteriform eruption that developed is described as segmentally arranged on the right side of the thorax. It was accompanied with fever. No mention is made of pain or of the subsequent course of the patient. Vesicular fluid produced keratitis in two of three rabbits and after repeated passages on the rabbit cornea proved to be encephalitogenic when inoculated by the corneal route. Inclusion bodies were seen in sections of the cornea but no mention is made of their presence in the nervous system. No immunologic investigations were carried out.

Herpes of the Fingers. Nicolau and Poincloux[29] reported the case of a thirty-two year old female who had experienced several recurrences of herpes of the right index finger over a period of six years. The later episodes were usually preceded by neuralgic pain about the right shoulder and in the right arm. No lymphadenopathy accompanied the eruption. The first attacks were mistaken by several physicians for pyogenic infections and the swelling of the finger was treated by incision. An agent

capable of causing keratoconjunctivitis and encephalitis in rabbits was obtained during two of the recurrences. Although the lesions produced in the cornea and the brain of the animals are said to have been typically herpetic, no specific mention of inclusion bodies is made. No immunologic studies were done.

The case reported by Gougerot and Blum[30] was that of a twenty-eight year old male whose initial lesion of the right middle finger followed soon upon a minor local injury. The initial lesion was not seen by the authors and whether it was accompanied by neuralgic pain is not stated. Recurrences, which were frequent, usually took the form of a bullous eruption of the terminal phalanx attended by median nerve neuralgia. Lymphangitic streaking of the forearm and enlargement of the epitrochlear node were noted. Following inoculation of material from the lesion of the finger on the cornea of a rabbit the animal developed keratitis which did not, however, become apparent for ten days. Paralysis of the hind legs of the animal occurred three days later. No other studies were carried out.

The foregoing sixteen cases are all that we have been able to find in which there is any reason to suspect that simplex virus may have been transferred to animals from a zoster-like eruption of man. Although it must be admitted that several of them are open to question, it is not unlikely that simplex virus was actually the cause in most of them. In all of them, certainly, the reaction of the experimental animals was quite different from the refractory state that could have been anticipated had they been true zoster.

MATERIALS AND METHODS

Isolation and Identification of the Virus. The technic of transfer of simplex virus from patients to animals was the same in every case. An area of vesiculation was swabbed lightly with acetone and allowed to dry. Several vesicles were then opened with a sterile needle and their contents taken up on the tip of a small, sterile swab of cotton which was also rubbed over the base of the vesicles. When not used promptly the swab was placed in the refrigerator, sometimes for several hours. After prior treatment with 5 per cent cocaine the cornea of a domestic hybrid rabbit was scarified by gentle cross-hatching with a cataract knife. The swab was then rubbed over the surface of the cornea. The animal was inspected daily. Within a day or two of the time keratitis could first be definitely discovered, the conjunctival sac was washed with a small quantity of Locke's solution and the washings were injected intracerebrally in mice or were inoculated upon the cornea of a second rabbit; in some instances the washings were passed to both mice and rabbits.

If the rabbit receiving the primary inoculation died of encephalomyelitis, its brain was removed and fixed in acetic acid—Zenker's solution. Sections of the pons and medulla were stained by the Giemsa technic and studied for inclusion bodies.

If the rabbit of the primary inoculation survived, it was tested from four to six weeks later for immunity to a known strain of simplex virus. The challenge inoculations consisted of the intracerebral injection of 0.1 ml. of a 10 per cent suspension of the HF strain[31] maintained by brain-to-brain passage in mice. The potency of the virus used to test immunity was demonstrated simultaneously by the intracerebral injection of mice. Rabbits inoculated on the cornea with washings from the eyes of those used for primary transfer were killed twenty-four to thirty-six hours after the appearance of keratitis and the cornea was removed, fixed and stained for microscopic study.

Mice inoculated intracerebrally were permitted to die of encephalomyelitis. The brains were removed, tested for the presence of bacteria by aerobic and anaerobic culture and after trituration passed to additional mice. After two or more passages in mice the brains were preserved in 50 per cent buffered glycerol for further study should the need arise. (It is of interest that in Case

IV the virus was isolated by direct intracerebral injection of mice as well as by corneal inoculation of a rabbit.)

Neutralization Tests. The capacity of the serum of each patient to neutralize the virus of herpes simplex was determined by mixing 0.5 ml. of the serum with an equal volume of decimal dilutions (10^{-1} to 10^{-7}, inclusive) of the HF strain. The mixtures were allowed to stand at room temperature for ninety minutes and then placed in the refrigerator for thirty minutes, after which they were tested for neutralization by injecting them intracerebrally in mice. Three mice were used for each dilution of the virus. The tests were controlled simultaneously by treating mixtures of the same dilutions of the virus and normal rabbit serum in the same manner. The patients' serums were obtained at the same time the eruptions were studied for viral content. In some instances neutralization tests were also done with serum obtained again several months later but, since the neutralizing power did not differ significantly from the serum of the first bleeding, they are not reported further.

All the data relative to transfer and identification of simplex virus from the five cases studied are presented in Table I. Included in the table, too, are the results of the neutralization tests. The capacity of each patient's serum is expressed in terms of the LD_{50} of the virus neutralized by 1 ml. of serum. This value is obtained by subtracting the logarithm of LD_{50} of the virus plus the patient's serum from the logarithm of LD_{50} of the virus plus normal rabbit serum.*

In the following summaries of cases the pertinent data are given up to the time the patients were first seen by us and our viral studies were done.

* Thus if the 50 per cent end point (LD_{50}) of the virus plus normal rabbit serum were $10^{5.75}$ and that of the virus plus the patient's serum $10^{1.5}$, the neutralizing power of the patient's serum, in terms of LD_{50}, would be the difference between the two values: $10^{4.25}$ or 18,000. Since each mouse received a total intracerebral inoculum of 0.03 ml., of which 0.015 ml. were viral antigen and the rest serum, the LD_{50} of virus neutralized by 1.0 ml. of the patient's serum would be $18{,}000 \times \frac{1}{0.015}$ or 1,188,000.

CASE REPORTS

Zosteriform Eruption of the Trigeminal Area

CASE 1. A sixty-one year old male physician was seen, with the following history: At the age of seventeen he had a very painful vesicular eruption that involved almost the entire skin surface supplied by the first branch of the fifth cranial nerve on the left side. Keratitis did not accompany the first or any of the many subsequent attacks. Medical advice was sought during the initial attack and a diagnosis of "shingles" was made. The second attack, almost as extensive as the first and like it in character, occurred six years later. Since then there have been recurrences at intervals of approximately twelve or eighteen months. The extent of the recurring eruptions has gradually diminished and in recent years it has been limited to the eyebrow and upper lid. A typical attack always starts with severe left-sided temporal and parietal pain usually of a neuralgic character. After about forty-eight hours vesiculation appears accompanied with a local stinging sensation and followed by edema of the upper lid. The homolateral, preauricular lymph node always becomes enlarged and tender. For two or three days after the appearance of the rash there is vague discomfort in the head, stiffness of the neck muscles on the left side and mild malaise.

Zosteriform Eruptions of the Trunk and Extremities

CASE 2. A thirty-six year old female was seen who for about three years had been subject to a recurring vesicular eruption over the posteromedial surface of the upper portion of the left thigh, a zone corresponding to the lower extremity of the dermal distribution of S_3. The area over which the rash occurred measured 3 by 4 cm. and was scarred and pigmented. The rash made its first appearance following a minor injury to the spine and had recurred eight or ten times each year. At times it coincided with menstrual periods but as often it did not. The patient believed that it was sometimes precipitated by infections of the respiratory tract and consistently by aspirin. The attacks were always preceded by intense neuralgic pain in the region of the skin involved, pain that persisted for two or three days after the eruption

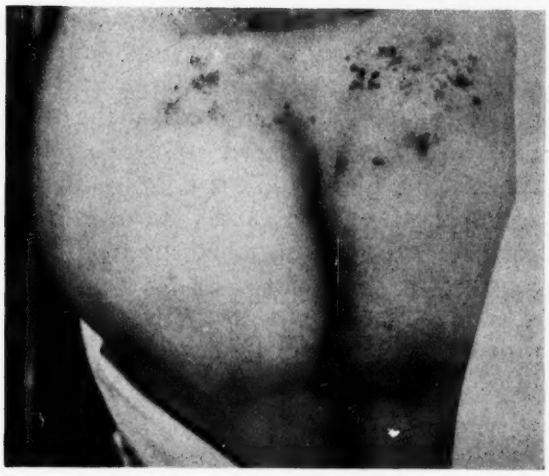

FIG. 1. Zoster-like eruption corresponding principally to the metamere D_{12}. The lesion which was accompanied by herpes labialis appeared during the course of meningococcal meningitis. Herpes simplex virus was recovered from vesicles.

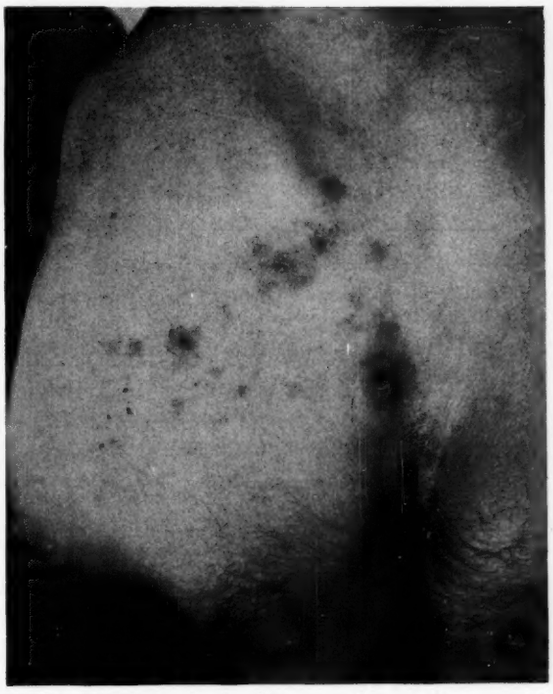

FIG. 2. Recurrent zoster-like eruption of the buttock corresponding to S_3. Herpes simplex virus was recovered from vesicles.

became manifest. Roentgenograms of the spine were negative. The patient denied having had oral or genital herpes in the past.

CASE 3. A male sixty-eight years of age was admitted to the hospital because of meningococcal meningitis. He had been ill for five days. Recovery followed treatment with sulfadiazine by mouth and penicillin administered both intramuscularly and intrathecally. On admission and before chemotherapy was begun the patient had herpes labialis and an herpetiform eruption of the back bilaterally at a level corresponding principally to D_{12}. (Fig. 1.) He complained of dull aching in the back over the area involved by the eruption. He had had labial herpes repeatedly over the course of many years but stated quite definitely that he had never before had a similar lesion of the back. No history of genital herpes could be obtained.

CASE 4. A male fifty-four years of age was seen who had a lung abscess. Treatment by the intramuscular injection of penicillin was given soon after a diagnosis was established. On the seventh day of penicillin therapy a vesicular rash appeared over the right buttock, accompanied at its onset with local itching and aching. The distribution of the rash corresponded incompletely to S_3. (Fig. 2.) Several weeks later in preparation for lobectomy he was given penicillin as an aerosol and eight days later developed a similar eruption in the same area, again attended by itching and aching. A third eruption of almost identical character and distribution occurred two months after lobectomy at a time when he was once again receiving penicillin intramuscularly. This second recurrence followed the institution of penicillin therapy by ten days. Before the appearance of the rash on this occasion care had been taken to avoid the injection of penicillin into the buttock on the affected side. It was during this last episode that simplex virus was isolated and the patient's blood serum was first studied for specific antibodies. The patient had no recollection of having had labial or genital herpes. He was certain that prior to the episodes described herein he had not had a similar lesion of the buttock.

Herpes of the Finger

CASE 5. A six year old male was brought to the hospital because of meningitis due to Hemophilus influenzae. Response to treatment with sulfadiazine and streptomycin was rapid. Four days after admission to the hospital he developed aphthous stomatitis, perioral herpes and painful swelling of the right middle finger. The finger was studded with small vesicles. The pain in the digit was entirely local and seemed to be due to distention of the tissues. Nothing interpretable as radicular pain or neuralgia subsequently developed. The patient's mother

had no recollection of his having had stomatitis or labial herpes previously. About two years before the right middle finger had received a crushing injury and had been swollen and very tender for about ten days. The mother was unable to recall whether vesicles had been present on the skin of the finger at that time.

COMMENTS

Of sixteen cases of zoster-like disease caused by simplex virus gathered from the literature and the five herein reported, a trigeminal area was involved in four, the thorax in four, the area supplied by the lower dorsal, the lumbar and the sacral roots in nine, an arm in one and a finger in three. In most of the reports there is no accurate statement of the extent of the eruption on the skin but in many of them it is said to have been zoster or to have resembled zoster. In one case the eruption was bilateral. In five of the twenty-one patients the dermal manifestations of the infection were preceded or accompanied by neuralgic pain. Data concerning the cerebrospinal fluid are reported in only one case in which mild lymphocytic pleocytosis was present. There was no clinical evidence of involvement of the spinal cord or of the brain in any of the cases nor was there any opportunity to make histopathologic studies of the posterior root ganglia or other nervous tissues. There were extraneous events that seemed to precipitate the disease in seven cases, namely, pneumonia in one, meningitis in two, injury of the spine in one, trauma at the site of the rash in one, the ingestion of aspirin in one and the administration of penicillin (on each of three different occasions) in one. Of all the cases only four are known to have had perioral or genital herpes previously. The sex of the twenty-one patients is given in sixteen instances; thirteen were males and three were females.

The frequency with which various areas of the skin are involved by zoster-like simplex infections may be the clue to the pathogenesis of the disease. Freund,[3] evidently basing his opinion largely upon clinical observations, states that zosteriform eruptions due to simplex virus are most common in the trigeminal area and that portion of the skin supplied by the sacral roots of the spinal cord (gluteal), an arrangement quite different from that of zoster itself which usually involves those parts of the skin supplied by the dorsal roots.[32]

While Freund's statement cannot be proved on the basis of the small number of cases from which it is at all reasonable to think that simplex virus has been isolated, it is not unlikely true. In the first place, and quite apart from its zosteriform manifestations, the sites most frequently infected by simplex virus are the mouth, the perioral skin and the genital area in both male and female. The former areas receive their sensory innervation by the trigeminal nerves and the genital area by certain of the sacral roots. Secondly, it is at least possible that the virus occasionally pursues local nerves from the skin and mucous membranes in man just as it has been shown to do in experimental animals. Thus one might expect that if human nervous tissues are infected by the virus, it would be those sensory ganglia the axons of which supply the mouth, the perioral skin and the genital regions that would be primarily concerned. Whether the virus in a dorsal ganglion may spread to adjoining posterior root ganglia is speculative but may be possible. Furthermore, it becomes not unreasonable to suppose that once the virus is within the cells of a sensory ganglion it exhibits the same character of latency (and therefore of recurring activity) that it is presumed to do in the skin. Finally, one would be led to think that at times of renewed activity the virus migrates centrifugally along the sensory root to produce in some individuals segmentally arranged skin eruptions resembling those of zoster.

A similar speculation has been made by Goodpasture[33] who suggested that in the intereruptive phases of simplex infection in the domain of the trigeminal nerve (herpes febrilis) the virus is perhaps har-

bored in the gasserian ganglion rather than in the skin. A systematic study of the gasserian ganglia of man with reference to infection by herpes simplex virus has not been made. In 1905 Howard[34,35] reported histopathologic observations of the gasserian ganglia of three patients who had recent lesions of herpes simplex on the face at the time of death. In all three the homolateral ganglion showed changes similar to those that Head and Campbell[1] had described a few years previously in the posterior root ganglia of classical, segmental zoster. An observation similar to that of Howard has recently been made by Freeman.[36]

The suggestion of Freund that zoster-like lesions caused by simplex virus occur most frequently over those parts of the skin supplied by the trigeminal nerves and the sacral roots is in keeping with the known facts if one may make the reasonable assumption that the virus pursues the axons of the local nerves. The lack of opportunity for detailed anatomic study and the relatively small number of reported cases in which simplex virus has been recovered from zosteriform eruptions do not permit an unqualified statement. In eight of the cases previously reported and in three of our own either the trigeminal or sacral roots are implicated; this constitutes more than one-half the total.

Several cases of encephalomyelitis in man have been proved to have been caused by simplex virus.[8] In none of them has involvement of the central nervous system been known to have been accompanied or immediately preceded by herpes of the skin or mucous membranes. This fact also makes it seem possible that in the intervals between its eruptive phases the virus may be harbored in nervous tissues remote from the epithelial surfaces of the body.

An added reason for entertaining the belief that zosteriform simplex infections of the skin owe their peculiar distribution to the prior involvement of certain of the sensory ganglia is the occurrence of neuralgic pain in several of the cases. This feature was unequivocal in Cases 1 and 2 of the present report and in the second case described by Luger and Lauda.[23] That it is inconstant does not detract from its significance for pain is by no means an invariable accompaniment of true zoster in which, it seems safe to say, the sensory ganglion is always involved. Neither does limitation of the eruption to only a portion of that area of skin supplied by a particular sensory root lessen the validity of the conception for the same is also true of zoster.

It is in its frequently recurrent nature that the zosteriform disease due to simplex virus differs sharply from zoster. As has already been pointed out, the varied manifestations of infection by simplex virus are notoriously recurrent whereas recurrence of true zoster is generally conceded to be a rarity.[8,32] It is tempting to speculate that some of the cases of so-called "symptomatic" zoster that follow upon such diseases as spinal injury, tumors of the spinal cord, leukemia, tabes dorsalis and meningitis may prove to result from latent infection of the posterior root ganglia by the virus of herpes simplex. Akin to this is the likelihood that in some of the cases of zosteriform simplex reviewed and reported herein the disease was precipitated by factors that are known to provoke simplex virus from its latent state, namely, various fevers and the administration of certain drugs.

Freund[3] has implied that simplex infections of the fingers should be considered zosteriform. The present authors are inclined to the opinion that the pathogenesis of the digital eruptions is, as a general rule, different from that of the zosteriform lesions produced by simplex virus elsewhere in the skin. It seems not unlikely that they usually arise not by centrifugal migration of the virus along a nerve trunk from a sensory ganglion to the skin but rather as a result of direct, local inoculation. To put an injured finger in one's mouth is common enough. Should simplex virus be present in the saliva, superinfection might occur. Patients with recurrent herpes simplex have been shown to develop specific lesions when fluid from their own herpetic vesicles is deliberately injected into a region of the skin

removed from the site of the recurrent eruption.[16,37] The neuralgic pain that has accompanied some of the cases of herpes simplex of the fingers might be due to centripetal spread of the virus along nerve trunks toward the central nervous system.

SUMMARY

Five patients presenting a zoster-like eruption are described. The virus of herpes simplex was isolated from the cutaneous lesions of each patient. A possible explanation of the pathogenesis of zosteriform disease caused by simplex virus is suggested. Further evidence of the neurotropism of the virus of herpes simplex in man is offered.

TABLE 1

TRANSFER TO ANIMALS AND IDENTIFICATION OF HERPES SIMPLEX VIRUS FROM ZOSTER-LIKE LESIONS OF MAN

SPECIFIC ANTIBODIES IN SERUM OF PATIENTS

No. of Case	Site of Lesion	Direct Transfer from Human Source to Cornea of Rabbits		Rabbit-to-rabbit Transfer by Corneal Inoculation	No. of Intracerebral Passages in Mice	LD_{50} of HF Virus Neutralized by 1 ml. of Patient's Serum
		Result	Subsequent Inoculation of HF Virus Intracerebrally			
1	Trigeminal	Keratitis; died of encephalitis; inclusion bodies in brain	.....	.....	2	42,000
2	Sacral 3	Keratitis; died of encephalitis; inclusion bodies in brain	.....	.....	7	1,200,000
3	Dorsal 12	Keratitis; died of encephalitis; inclusion bodies in brain	.....	Keratitis killed; inclusion bodies in corneal epithelium	3	400,000
4	Sacral 3	Keratitis; no clinical evidence of encephalitis	Immune	Keratitis killed; inclusion bodies in corneal epithelium	8	1,200,000
5	Finger	Keratitis; no clinical evidence of encephalitis	Immune	Keratitis killed; inclusion bodies in corneal epithelium	None attempted	700,000

In none of the five cases reported herein is the zosteriform eruption known to have been a primary infection. That all of the patients had had their initial infection by simplex virus before they were studied by us is obvious from the measurements of circulating antibodies against the virus. (Table 1.) As reference to the table shows, every patient possessed a significant titer of specific neutralizing antibodies at the time he or she was first seen. Only in Case 3 was there reason to think that the initial zosteriform lesion was studied and this patient is known previously to have had recurrent herpes of the lips. Whether or not zoster-like lesions due to simplex virus may occur during or soon after a primary infection by the virus must remain unanswered for the present.

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Cause of Death in Meningococcic Infection*

Analysis of 300 Fatal Cases

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SINCE Vieusseaux[1] first described epidemic meningitis in 1805 outbreaks of this disease have occurred during every war. Within a few months of mobilization in World War I a sharp epidemic of the disease had begun. In World War II mobilization began in September, 1940, but not until December, 1942, did meningococcic infections reach epidemic proportions among American troops. Figure 1 charts admissions to Army hospitals in the United States by months in both World Wars, with ratios per 1,000 of strength in relation to the time of mobilization.[2,3] During World War I there were 2,466 soldiers with this infection admitted to hospitals in the continental United States. Of these 825 died—a case fatality rate of 33 per cent.[2] The case fatality rate for the entire army at home and abroad was approximately 39 per cent. During the second World War from January, 1940, to September, 1945, 11,032 instances of this infection occurred in this country with only 396 deaths—a case fatality rate of 3.6 per cent.[3] Figure 2 shows the case fatality rates in both wars by months.[2,3] Over the same period there were 14,504 admissions to Army hospitals throughout the world for meningococcic infection, with 557 deaths—a case fatality

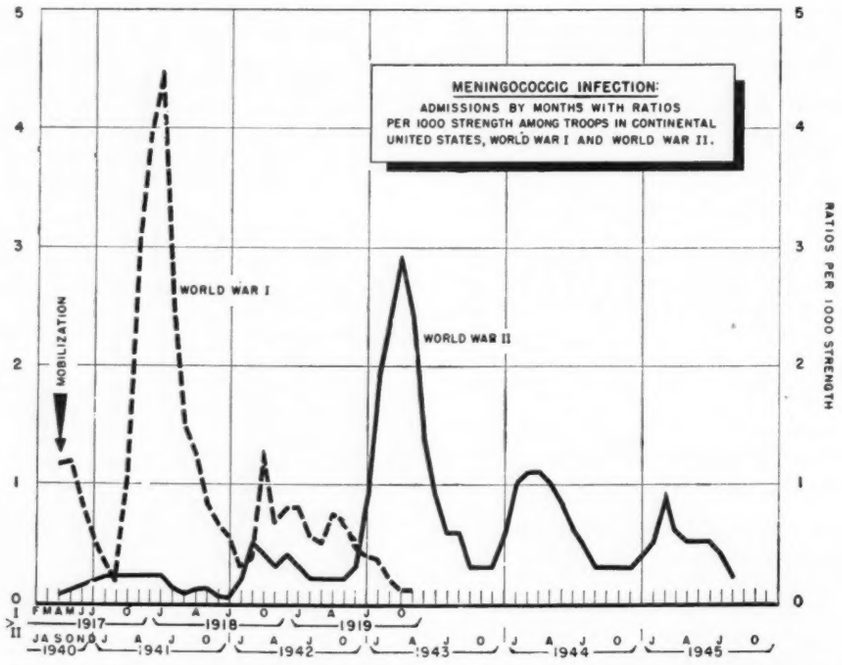

FIG. 1. Admissions by months with ratios per 1,000 strength among troops in continental United States, World War I and World War II.

* Read before the sixty-first annual meeting of the American Clinical and Climatological Association at Hot Springs, Va., November 10, 1948.

rate of 3.8 per cent. This includes patients treated on all fronts with the inherent difficulties of transportation and care in forward, mobile hospitals and those treated in installations in the peaceful zone of the interior. The fatalities per 100 patients in Wars is a direct result of sulfonamide therapy. The decreasing mortality during each year of the last World War reflects the growing experience of medical officers with the infection, resulting in its early recognition and prompt, adequate treatment.

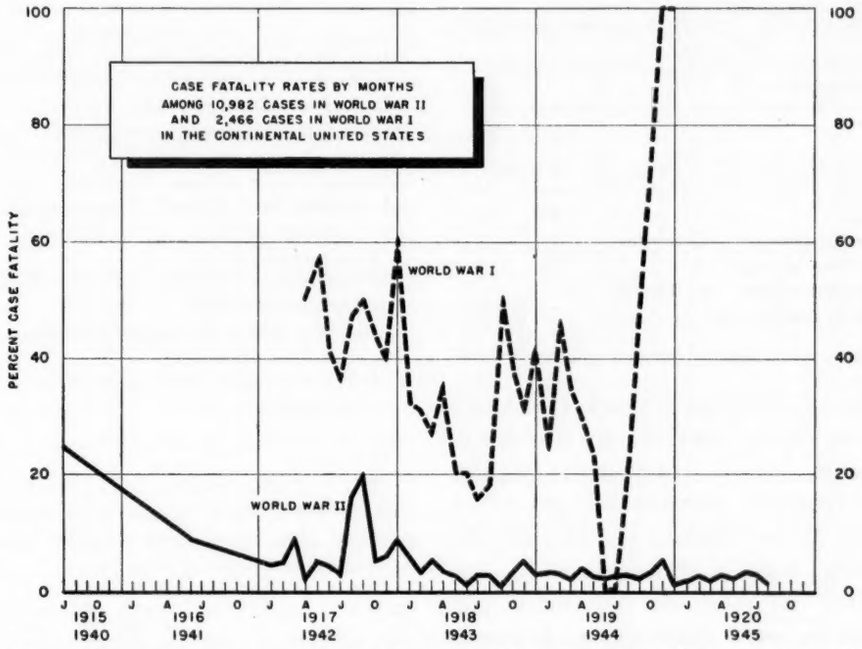

FIG. 2. Case fatality rates by months among 10,982 cases in World War II and 2,466 cases in World War I in continental United States.

TABLE I

NUMBER OF DEATHS BY YEARS DUE TO SERIOUS INFECTIOUS DISEASES AND ANNUAL DEATH RATES PER 100,000 OF TROOP STRENGTH FOR THE ENTIRE PERIOD

Year	Lobar Pneumonia	Atypical Pneumonia	Malaria	Scrub Typhus	Hepatitis	Bacillary Dysentery	Amebic Dysentery	Meningococcic Infections
1942.....	52	38	24	....	81	2	6	73
1943.....	120	48	110	49	6	6	4	268
1944.....	126	58	75	180	61	3	6	127
Total.....	298	144	209	229	148	11	16	468
Annual rate per 100,000 troops.	1.82	0.88	1.28	1.40	0.91	0.07	0.10	2.86

the continential United States for the years of mobilization and war were as follows: 1940, 30; 1941, 8.4; 1942, 7.4; 1943, 3.6; 1944, 2.5 and 1945, 2.4.[3]

The gratifying reduction in mortality of from 39 to 3.8 per cent in the two World

In spite of the large number of soldiers ill with this disease relatively few died. However, Table I shows that even with a remarkably low case fatality rate, meningococcic infections killed more soldiers than any other infectious disease and that death

rates per 100,000 of troop strength were higher than that of any other infectious disease.[3]

It seemed worth while to attempt to ascertain the cause of death in the fatal instances of meningococcic infection. Through the courtesy of Colonel James E. Ashe, Director of the Army Institute of Pathology, and of Major Webb Haymaker of the Staff of that Institute, the autopsy protocols and abstracts of the clinical records of 300 patients dying with this infection in the United States were made available for study. The cases were analyzed as to cause of death, duration of illness from admission to death and, as far as possible, as to type of treatment used. Certain other observations will be reported. Table II, which records the incidence of deaths resulting from the three major forms of the infection, shows that more patients died from the fulminant forms of bacteremia than from meningitis.

TABLE II

FORMS OF MENINGOCOCCIC INFECTION CAUSING DEATH IN 300 CASES

	Number	Per cent
Meningitis	144	48
Fulminant meningococcic bacteremia with adrenal hemorrhage	126	42
Fulminant meningococcic bacteremia without adrenal hemorrhage	30	10

ANALYSIS OF THE DEATHS FROM MENINGITIS

Of the 144 patients who died from meningitis, only twenty-six lived ninety-six hours or longer. The duration of life in this group of twenty-six patients ranged from four to 110 days. Table III shows the apparent cause and factors contributing to death in this group. It will be seen that in two-thirds of those a complication caused or contributed to death.

It appears from the data in Table IV, which shows the duration of life in relation to the severity of meningitis at necropsy, that in general those patients with the more severe meningeal involvements tended to live longer than those with moderate involvement. It is believed this indicates that since the advent of sulfonamide therapy death is most commonly due to the effects of bacteremia and resulting "toxemia" during the early phase of the illness rather than to the meningitis itself.

TABLE III

MENINGITIS

CAUSE OF DEATH AND COMPLICATIONS CONTRIBUTING TO DEATH IN 26 PATIENTS WHO LIVED 96 HOURS OR LONGER

Meningitis, uncomplicated	9*
Meningitis with meningoencephalitis	3
Meningitis with complicating pneumonia	4
Meningitis with adrenal infarction	1
Myocarditis after recovery from meningitis	1
Brain abscess due to N. intracellularis after recovery from meningitis	1
Hemoglobinuric nephrosis after transfusion	1
Sulfonamide nephrosis	3
Pulmonary infarct during convalescence	1
Multiple lung abscesses	1
Fulminant meningococcic sepsis after recovery from meningitis	1
Total	26

* One of these patients was treated inadequately on the seventh day of the disease and in one sulfadiazine was stopped after initial good response because of the assumed development of drug fever.

TABLE IV

MENINGITIS

DURATION OF LIFE FROM ADMISSION TO DEATH IN 118 PATIENTS LIVING LESS THAN 96 HOURS IN RELATION TO THE GRADE OF MENINGITIS AT AUTOPSY

Severity	No.	Per cent	No. of Patients on Whom Data Available	Hours Admission to Death		
				Average	Maximal	Minimal
Moderate	10	8	10	23	62	1
Severe	93	80	93	38	95	1
No record	15	12	10	30	90	2
Total	118	100	113	31	95	1

Among the 118 patients who died within ninety-six hours of admission, certain associate lesions were found at autopsy. These were pneumonia in twenty-six, encephalitis in eleven, myocarditis in eleven, purulent pericarditis in four, pressure cone in four,

periadrenal hemorrhage in two, tubular degeneration of the adrenal, meningococcic peritonitis, purulent arthritis, subarachnoid hemorrhage and bleeding peptic ulcer each in one of the patients.

The records of treatment available in the clinical abstracts of the 144 patients from meningitis were not complete so that the total dosage administered is not known. Sulfadiazine was used in 103, sulfathiazole in thirteen, sulfapyridine in two, sulfanilamide in four and antimeningococcic serum alone in one of the cases. In nine there was no record of treatment and in twelve no specific therapy was given. Forty-two patients received other therapy in addition to sulfonamides, namely, antimeningococcic serum fourteen, meningococcus antitoxin fifteen and penicillin thirteen. In fifty-five of the 144 cases there were records of the sulfonamide concentration in the blood. The maximal concentrations in these was 52, the average 17 and the minimal 3.5 mg. per 100 cc. of blood. It would appear that at least adequate dosages of sulfonamides had been given to these patients. Six patients were either undiagnosed or diagnosed incorrectly prior to necropsy.

ANALYSIS OF THE DEATHS FROM BACTEREMIA

More than half of the fatal instances of meningococcic infection resulted from bacteremia. The blood culture was positive for N. intracellularis in 94 per cent of the cases in which a blood culture report was available. Hemorrhage into the adrenal was present in 126 and absent in thirty of these deaths from bacteremia.

Adrenal Hemorrhage Group. In all patients recorded as having hemorrhage into the adrenal gland there was free blood, and no instance of hyperemia is included. Table v indicates that the duration of life in the 126 cases is in inverse proportion to the degree of hemorrhage found at autopsy. Those with minor grades of hemorrhage into the adrenal lived on the average forty-eight hours after admission to hospital while those with moderate and massive hemorrhage lived an average of twenty-two and sixteen hours, respectively.

Patients with adrenal hemorrhage survived from a few minutes to 120 hours after admission. Myocarditis was found on microscopic study of the heart in twenty-eight

TABLE V
BACTEREMIA
DURATION OF LIFE IN PATIENTS WITH ADRENAL HEMORRHAGE IN HOURS, ADMISSION TO DEATH, IN RELATION TO SEVERITY OF HEMORRHAGE

Grade of Hemorrhage	No.	Per cent	No. of Patients with Data for Analysis	Hours		
				Average	Maximal	Minimal
Mild	21	16.7	20	48	120	1¾
Moderate	47	37.3	44	22	60	⅙
Massive	56	44.4	53	16	49	1
No record	2	1.6	1	53	53	53
Total	126	100.0	118	21	102	⅙

TABLE VI
ERRONEOUS DIAGNOSIS OR NO DIAGNOSIS MADE PRIOR TO AUTOPSY IN 300 DEATHS

Diagnosis	Meningitis Group	Bacteremia Group	
		With Adrenal Hemorrhage	Without Adrenal Hemorrhage
No diagnosis	2	4	5
Rocky Mountain spotted fever	..	3	..
Endemic typhus	1	1	..
Heat stroke	..	2	..
Acute leukemia	..	1	..
Purpura hemorrhagica	..	2	..
Malaria	1	..	..
"Pachymengitis"	1	1	..
Psychosis	1	..	..
Total	6	14	5
Per cent not or erroneously diagnosed	4	11	16

(22 per cent) of the patients. It is not surprising, considering the previous rarity of Waterhouse-Friderichsen syndrome, that fourteen cases (11 per cent) were either incorrectly diagnosed or not diagnosed prior to death. Table VI indicates the erroneous diagnoses made in these patients and in

those with meningitis and bacteremia without adrenal hemorrhage.

In the Waterhouse-Friderichsen syndrome the manifestations of meningitis are usually absent or slight. In almost half of the 126 patients dying with this syndrome there was no meningitis present at necropsy. In an additional 37 per cent meningitis was of mild grade. Less than 15 per cent of the autopsies showed evidence of a moderate or severe grade of meningitis. Table VII shows the grade of meningitis, if present, in this group.

TABLE VII
SEVERITY OF MENINGITIS AT AUTOPSY IN 156 PATIENTS WITH FULMINANT BACTEREMIA

Severity of Meningitis	Bacteremia with Adrenal Hemorrhage	Bacteremia without Adrenal Hemorrhage
None	61	13
Slight	48	16
Moderate	7	..
Severe	7	..
Unclassified	1	..
No record	2	..
Total	126	30

Hemorrhage into the adrenal was found at autopsy in five patients who during life did not have the usual manifestations of Waterhouse-Friderichsen syndrome. Conversely, among the thirty patients who died from fulminant bacteremia in whom no adrenal hemorrhage was found, four patients had shown the classical clinical manifestations of the syndrome. Thomas[4] has reported three of these cases. These observations indicate that in fulminant meningococcic bacteremia it is difficult if not impossible to be certain on clinical grounds whether or not adrenal hemorrhage has occurred.

In this group of patients the abstracts are again not adequate to give a complete record of all treatment given. However, of the 126 patients, twenty-three received no specific therapy; for nine there is no record of treatment; for eighty-three sulfadiazine was used and in eleven others some other sulfonamide was employed. The average amount of sulfadiazine given on the first day of treatment was 10, the maximal 26 and the minimal 4 gm. Sulfadiazine blood concentrations were recorded in only eighteen patients and ranged from 3.5 to 56 with an average of 16 mg. per 100 cc. of blood. The records of additional forms of therapy are not complete so that the number of patients receiving aqueous adrenal cortical extract, antitoxin, penicillin, plasma, etc., is not known.

Bacteremia without Adrenal Hemorrhage. Thirty patients, 10 per cent of all those dying with meningococcic infection, had bacteremia without hemorrhage into the adrenal and with slight or no involvement of the meninges. In sixteen there was only slight meningitis at autopsy and in thirteen there was no evidence of meningitis. (Table VII.) In one case information as to meningeal infection was not available. A diagnosis was not arrived at prior to death in five cases (16 per cent). The blood culture had been positive in 75 per cent of the patients on whom reports were available. This group of patients survived for from two to 101 hours and died on the average thirty-three hours after admission. At necropsy diffuse hemorrhages into the serous membranes and hemorrhages into the lungs and other organs not including the adrenals were usual. The treatment in this group was comparable to that given to the group with adrenal hemorrhage. Eighteen of the thirty patients received sulfadiazine. In only five patients was there a record of sulfadiazine concentration in the blood. These were 25, 19, 22, 9 and 5 mg. per 100 cc. of blood.

COMMENTS

It would appear from an analysis of these data that when meningococcic infection is treated early with sulfonamides, meningitis is not often the sole cause of death. Those patients with meningitis who died in less than ninety-six hours probably succumbed to bacteremia and the accompanying "toxe-

mia" as much as to the meningitis. The majority of those who lived longer were found to have complications at the time of death. Bacteremia with minimal or no meningitis caused death in 156 of the 300 patients. In the group of 144 patients who died with meningitis 118 died in less than ninety-six hours. In general those who died most rapidly showed least meningitis at autopsy. It would appear, therefore, that bacteremia and concomitant "toxemia" either caused death or played a major role in the fatal outcome in 274 of the 300 deaths analyzed. This again emphasizes the necessity of recognizing that meningococcic meningitis begins as bacteremia. This phase of the disease can be diagnosed by an experienced clinician before the report of a blood culture is available. Treatment in this phase may lower death rates still further.

SUMMARY

An analysis of the cause of death in 300 fatal cases of meningococcic infection has been reported. Death resulted from bacteremia in 156 of these cases and in 126 of them hemorrhage into the adrenals was found at autopsy. Of the 144 patients who died from meningitis only twenty-six lived longer than ninety-six hours. It is suggested that in those who survived less than ninety-six hours bacteremia and resultant "toxemia" played as important a lethal role as did meningitis.

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Abdominal Pain in Dissecting Aneurysm of the Aorta*

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THE frequency with which an acute coronary occlusion may be mistaken for an "acute abdomen" is well known. The differential diagnosis can usually be made after a careful history and physical examination aided, of course, by the electrocardiogram. A dissecting aneurysm of the aorta may also simulate an "acute abdomen," and here the differential diagnosis becomes much more difficult. Cases have been misdiagnosed as acute pancreatitis, mesenteric thrombosis, perforated peptic ulcer, etc. Not infrequently such patients have been subjected to unnecessary abdominal surgery. Finkelstein and Jacobi[1] reported a case of dissecting aneurysm characterized by abdominal pain radiating through to the back. The antemortem diagnosis had been that of a perforated peptic ulcer. Kennedy[2] described a case in which the antemortem diagnosis was mesenteric thrombosis. At autopsy a dissecting aneurysm involving the superior mesenteric artery was discovered.

During the years 1935 to 1947 inclusive fifty-eight autopsy-proven cases of dissecting aneurysm originating in the thoracic aorta were observed at the Los Angeles County Hospital. These have been carefully reviewed as to mode of onset, type of pain, location of pain, etc.

Presenting Symptom and Mode of Onset. Pain was the presenting symptom in forty-five patients (77.6 per cent). Of this group the pain was located initially in the chest in seventeen (37.7 per cent) and in the epigastrium in fourteen (31.1 per cent). In the remaining cases the pain was described as being in both the epigastrium and lower chest (four cases), the interscapular area (four cases), the neck (three cases), the mid-back (two cases), and the sacrum (one case). (Table I.)

TABLE I
MODE OF ONSET IN FIFTY-EIGHT CASES OF DISSECTING ANEURYSM OF THE AORTA

Mode of Onset	No.
1. Pain	45 (77.6%)
Chest	17
Epigastrium	14
Epigastrium and low in chest	4
Interscapular	4
Neck	3
Mid-back	2
Sacrum	1
2. Syncope	8 (13.2%)
3. No history of pain or syncope	6 (8.6%)

Abdominal Pain. The number of patients (fourteen) with initial abdominal pain was only three less than those with initial chest pain (seventeen). The pain was most commonly described as sudden in onset, severe, ripping, tearing, excruciating, etc. In many cases the pain was so severe as to cause the patient to toss about restlessly or to double up in bed in an attempt to obtain relief. In others the patient would lie on the floor seeking relief. The statement not infrequently obtained was that it felt as if "something had torn loose in the abdomen." Occasionally the pain was throbbing in nature. This has been attributed to successive pulse waves

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splitting the media or distending the newly formed aneurysmal sac.

Radiation of the Initial Pain. In Table II the radiation of pain from the initial site has been recorded. The back was the most frequent site of radiation occurring in sixteen cases. Seven (50 per cent) of those patients with initial abdominal pain experienced the radiation of pain through to the back. In a similar number of cases with initial onset in the abdomen the pain radiated up into the chest.

TABLE II
RADIATION OF PAIN

Initial Location of Pain	Chest	Abdomen	Flanks	Neck	Back	Interscapular Area	Arms	Legs	Shoulders	Right Ear
Chest (17 cases)		3	1	2	5	1	1			
Epigastrium (14 cases)	7		2	1	7	2	1	1	2	
Mid-back (2 cases)		1					1	1		
Neck (3 cases)		1			1					1
Epigastrium and low in anterior chest (4 cases)					3			1		
Interscapular area (4 cases)		1	1				1	1		
Sacrum (1 case)										
Total	7	6	4	3	16	3	4	4	2	1

Radiation into the flanks occurred in four instances, two of these beginning initially in the abdomen. At postmortem this was found in all cases to have been due to dissection of one or both renal arteries with resultant thrombosis and renal infarction.

Radiation of pain into the extremities does not occur with as great a frequency as might be expected. In eight instances the pain was recorded as radiating into either upper or lower extremities.

Other Symptoms. In addition to the major presenting symptomatology, the minor or secondary complaints and symptoms have been recorded. (Table III.) Vomiting occurred in twelve instances, accompanied in each by abdominal pain. In eight of these at postmortem the dissection was found to have extended down into the abdominal aorta. In four of the five patients with oliguria the renal arteries were involved in the dissection. Melena occurred in two patients in one of whom the dissection had involved the superior mesenteric artery. In three patients with hemoptysis the dissection had extended along the pulmonary arteries into the roots of both lungs.

TABLE III
SECONDARY SYMPTOMS

Dyspnea	25
Vomiting	12
Nausea	6
Orthopnea	6
Oliguria	5
Hemoptysis	3
Ankledema	2
Melena	2
Hematemesis	2
Hematuria	2

Diagnosis in Patients with Abdominal Pain. Because of the frequency with which dissecting aneurysm had its onset with initial epigastric pain in this series, these cases were carefully reviewed and it was found that eight of the fourteen cases were found to have been diagnosed as "acute abdomen"

at the time of their admission to the Los Angeles County Hospital. (Table IV.)

Acute pancreatitis appears to be the condition most frequently confused with dissecting aneurysms of the aorta which have their onset with abdominal pain.

TABLE IV
DIAGNOSES IN EIGHT CASES OF DISSECTING ANEURYSM HAVING ONSET WITH ABDOMINAL PAIN

Initial Diagnosis	No. of Cases
Acute pancreatitis	4
Perforated peptic ulcer with acute pancreatitis	1
Mesenteric thrombosis	2
Intestinal obstruction	1

In this series there were five cases wrongly diagnosed as acute pancreatitis (one case secondary to or complicating a perforated peptic ulcer). All five of these patients had hypertension on admission. This differential diagnosis most likely arises more often than apparent from these figures, as Paxton and Payne[3] in a review of 307 proven cases of pancreatitis found hypertension in 19.5 per cent. Thus epigastric pain radiating to the back and flanks, accompanied by nausea, vomiting and hypertension not infrequently poses a difficult problem in differential diagnosis.

Usually the serum amylase and lipase enzyme determinations are relied upon to confirm the diagnosis of acute pancreatitis. Polowe[4] listed a large number of situations in addition to acute pancreatitis which will cause elevations of the serum amylase. Among these are trauma to the pancreas, perforated ulcer at or near the pancreas, mesenteric thromboses and aneurysms of the thoracic aorta. He reached the conclusion after 6,000 tests on 1,800 patients with various diseases that slight elevation of the serum amylase may occur secondary to other diseases but that moderate to marked elevation of the serum amylase usually means acute pancreatitis.

Of the five patients suspected of acute pancreatitis, serum amylase was determined in four. In two of these the serum amylase was elevated (300 and 500 units) and in the other two it was normal (70 and 10 units). The following two case histories have been chosen as exemplifying the difficulties encountered in this differential diagnosis. The first patient was thought to have a perforated peptic ulcer with an associated pancreatitis (amylase 300 units). Surgical exploration did not disclose any abnormality in the abdomen. At postmortem examination a dissecting aneurysm of the aorta was found which had dissected the superior mesenteric artery and had resulted in hemorrhage about the head of the pancreas.

CASE REPORTS

CASE 1. F. D., fifty-nine years of age, a white male, factory worker, was admitted on October 7, 1944. About 6:00 A.M. on the day of admission this man noticed the onset of severe sharp epigastric pain which caused him to double up and lie on the floor in an attempt to obtain relief. The pain was also felt high in the back in the interscapular areas and in both shoulders. The pain was made worse by deep breathing. There was a long past history of indigestion with questionable tarry stools of recent origin and hypertension of a few years' duration for which he stated he had been receiving intravenous arsenic. The patient denied ever having syphilis or gonorrhea.

Physical examination on admission revealed an acutely ill white male tossing about in bed and complaining of severe abdominal pain. His temperature was 98°F., pulse rate 84 per minute. Examination of the skin, head, eyes, ears, nose and throat showed no abnormality. The veins of the neck were normal; there was no adenopathy and the thyroid could not be felt. The lungs were clear to percussion and auscultation. Examination of the heart revealed that the point of maximum impulse was in the fifth interspace at the anterior axillary line. Sounds were of fair quality. There was an apical systolic murmur and a questionable diastolic murmur thought to be heard over the entire precordium; regular sinus rhytnm was present; his blood pressure was 280/150. The abdomen was flat and did not move with respiration. There was board-like rigidity in the upper quadrants and peristalsis was absent.

Laboratory data were as follows: blood count: white blood cells 10,000 (polymorphonuclears 93 per cent, lymphocytes 7 per cent); urinalysis was negative for sugar; albumin 2+; microscopic: 1 to 7 red blood cells per high power field;

several hyaline and granular casts; blood amylase 300 units (normal 80 to 150 units).

The admitting diagnosis was perforated peptic ulcer with the secondary possibility of an acute pancreatitis. The patient was taken to the operating room several hours after admission and an exploratory laparotomy performed. The findings at operation were all negative, with no discernible pathologic condition in the abdomen. On October 8, 1944, one hour after the operation, the patient suddenly expired.

The significant findings at necropsy were the following: The pericardium was normal. The heart weighed 650 gm. The valves were normal and their measurements were: aortic 9 cm., pulmonic 8 cm., tricuspid 12 cm. and mitral 10 cm. The wall of the left ventricle measured 20 mm. and the right 2–3 mm. The coronary vessels were moderately atherosclerotic but patent. There was evidence of tree-barking and stellate scars in the first portion of the ascending aorta. Arising at the level of the innominate artery was an aneurysm which had dissected distally down into both common iliacs. There were no intimal tears and no sites of external rupture. The dissection had involved the innominate and superior mesenteric vessels. Microscopically, the aorta revealed idiopathic, cystic medial necrosis.

There was marked dilatation of the stomach and of both large and small intestines. In some areas of the small bowel the wall appeared somewhat hemorrhagic. There was also some hemorrhage about the head of the pancreas. On sectioning the pancreas did not appear abnormal.

The second case presented had an elevated serum amylase of 500 units on admission. At postmortem the dissecting aneurysm had extended down to the level of the diaphragm and the pancreas appeared normal.

CASE II. R. S., seventy-two years of age, a white female housewife, was admitted on November 26, 1946. About 11:30 P.M. the evening prior to admission this patient was awakened by the sudden onset of severe abdominal pain which was so excruciating that she was unable to sleep and walked the floor the entire night. The pain radiated through to her mid-back and also was described as radiating down the inner aspect of her left arm. Other complaints were those of nausea, vomiting and hemoptysis. She had suffered a cerebrovascular accident in 1940.

On admission her temperature was 98.6°F., pulse rate 72 per minute and respirations 24 per minute. The skin of the extremities was cold and sweaty. No jaundice was present. Examination of the eyes, ears, nose, neck and chest revealed no abnormalities. The heart showed grade 3 enlargement; the sounds were of fair quality. A grade 3 precordial systolic murmur was heard best at the mitral area. Her blood pressure was 240/110. The abdomen was slightly distended but not rigid; deep epigastric tenderness was present and peristalsis was normal. The liver and spleen could not be felt.

Laboratory data were as follows: Blood count: hemoglobin 15 gm.; white blood cells 22,400 (polymorphonuclears 88 per cent, lymphocytes 12 per cent; serum amylase 500 units.

The admitting diagnosis had been acute pancreatitis. Approximately twenty-six hours after the onset of pain the patient expired suddenly. Significant findings at necropsy were as follows: The heart weighed 600 gm. The wall of the left ventricle measured 19 mm. and the right ventricle 4 mm. Just above the aortic ring there was a transverse intimal tear which communicated with a dissecting aneurysm of the aorta. The aneurysm was filled with fresh blood clot and extended distally to just above the diaphragm. At the level of the hilus of the left lung the aneurysm had ruptured through the adventitia resulting in a left-sided hemothorax. Grossly, the pancreas appeared normal; microscopically, it showed autolysis.

Two cases were thought to have mesenteric thrombosis on admission. In dissecting aneurysms extending down into the superior mesenteric artery this is a distinct possibility as illustrated by the Kennedy's case[2] previously described. Such an occurrence is not very common. The following case is that of a patient with acute epigastric pain accompanied by tarry stools thought to have mesenteric thrombosis. At postmortem the dissection had extended into the abdominal aorta to involve the celiac axis. Both small and large intestines appeared normal.

CASE III. L. W., a sixty-seven year old white male, was admitted on March 22, 1945, complaining of severe epigastric pain of forty-eight hours' duration accompanied by tarry stools. Other complaints were those of dyspnea and weakness. The patient's past history revealed nothing outstanding except the presence of hypertension of several years' duration.

Upon admission his temperature was 97.5°F.; pulse 88 per minute; respirations 22 per minute and blood pressure 70/50. There was marked pallor of the skin and mucous membranes and the extremities were cold and moist. The head, eyes, ears, nose and throat were normal. The veins of the neck were distended but not pulsating and filled from above. The lungs were clear. The size of the heart was not determined; sounds were only fair in quality; no thrills or murmurs could be heard. The abdomen was slightly distended; deep epigastric tenderness was present and peristalsis appeared diminished. Upon rectal examination a tarry stool was obtained. The non-protein nitrogen was 70 mg. per cent and the Wassermann reaction was doubtful.

This patient was admitted in shock with the diagnosis of mesenteric thrombosis. He gradually went downhill and died twelve days after admission.

At necropsy the heart appeared normal in size, weighing 340 gm. The aorta was diffusely enlarged from the beginning of the ascending aorta to a point 2 cm. below the coeliac axis. No intimal tears were found but a large blood clot had dissected the media from the beginning of the ascending aorta to below the celiac axis. Both large and small intestines appeared normal.

COMMENTS

The frequency of abdominal pain as a presenting complaint in dissecting aneurysm of the aorta should bring forth a consideration of this diagnosis in patients with severe abdominal pain and hypertension. In order to facilitate the diagnosis a search should be made for the diagnostic features of a dissecting aneurysm. These are summarized as follows:

1. The onset is usually sudden and dramatic with a history of severe agonizing pain in the chest or abdomen, radiating most often to the back or down into the abdomen. Radiation to the extremities is not common but of diagnostic value when present. Less often the onset may be with syncope or unconsciousness.

2. The clinical appearance of shock (cold sweaty extremities) is usually present with either lowered or elevated blood pressures.

3. Aortic diastolic murmurs were present in 27.5 per cent of the present series. The sudden appearance of an aortic diastolic murmur, in the presence of severe chest or abdominal pain, accompanied by a cylindrical dilatation of the ascending aorta is almost pathognomonic of dissecting aneurysm.

4. Inequalities of pulse and blood pressures, resulting from the dissection extending into the subclavian or femoral arteries (present in 20 per cent of the present series) are diagnostic features. Tenderness of vessels involved, palpable pulsating masses and ecchymosis about the large branches should be looked for.

5. Renal symptoms such as flank pain, hematuria, oliguria, etc., may be present. Such findings usually represent dissection of the renal arteries but may be due to primary renal disease.

6. Neurologic symptoms may be present (20 per cent of the present series). Interruption of the cerebral blood flow may produce an onset with syncope, dizziness, unconsciousness or hemiplegia. Transient weakness and anesthesia of one of more extremities may be caused by ischemia of peripheral nerve trunks or interference with the blood supply of the spinal cord.

7. The electrocardiogram is non-specific. Changes of coronary insufficiency, acute myocardial infarction, pericarditis, etc., may be present. The most common pattern encountered is that of left ventricular strain.

8. Roentgenology has limited value as these patients are usually too ill to permit adequate study of the mediastinum. Progressive or sudden increase in the shadow of the ascending aorta may facilitate the diagnosis.

SUMMARY

The onset of dissecting aneurysm of the aorta with severe epigastric pain has been discussed. Eight of fourteen such cases were diagnosed as having acute pancreatitis, mesenteric thrombosis, perforated peptic ulcer, etc.

In all patients with severe abdominal pain accompanied by hypertension the differential diagnosis should include dissecting aneurysm of the aorta.

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Review

Cardiac Aneurysm*

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CARDIAC aneurysm is one of the less frequent complications following myocardial infarctions. While the correct diagnosis is occasionally made, this disorder is often overlooked clinically and in the majority of cases the diagnosis is first discovered on the roentgenographic or postmortem examination. In an attempt to emphasize aids in the diagnosis of this lesion the literature is reviewed and in addition twenty-six cases of cardiac aneurysm proved by autopsy are presented from our records.

Following myocardial infarctions, resultant fibrosis and thinning occur and it is not uncommon for this sequence of events to lead to formation of a localized cardiac dilatation in the left ventricle. Since by definition an aneurysm is a sac formed as a result of focal weakness and distention of an artery, the term "localized ventricular bulge" rather than cardiac aneurysm should be used to describe such a lesion, as suggested by Schwedel and Gross.[1] However, the term cardiac aneurysm appears to have been accepted through the medium of common usage.

The varying incidence of cardiac aneurysm as reported by different investigators may possibly be due to difference in criteria used and in the selection of cases. In addition, some cases which exhibit localized ventricular bulging during life may fail to do so at the autopsy table. As Crawford[2] suggests, cardiac aneurysm refers only to "permanent localized bulging or during systole, a well marked localized expansion beyond the contour of the rest of the heart."

Earlier writers such as Baillow[2] (1538) used the term aneurysm in describing generalized cardiac dilatation. Lancisci[2] (1740) referred to localized thinning of the ventricular wall and Morgagni[3] (1681–1771) discussed aneurysm of the heart in their respective classifications of heart disease. In 1793 Mathew Baillie[4] described a case of ventricular aneurysm in a patient exhibiting an orange-sized bulge of the apical portion of the left ventricle, the pouch being lined with a thick, opaque membrane. Although the ventricular bulge contained no thrombus, Baillie added that it was more common to find coagulated blood in the aneurysms and that the "quantity of the coagulated blood in the aneurysm depends commonly on the size of the bag."

Corvisart (1806), in submitting a classification of heart disease, separated cardiac aneurysms into active and passive groups (referring to cardiac hypertrophy and dilatation respectively). In 1836 Laennec[5] wrote: "In certain cases the heart may be affected with partial and truly aneurysmal dilatation. M. Corvisart found in the person of a young negro who died of suffocation, an example of this affection. On the superior and lateral portion of the ventricle (the left) there was a tumour almost as large as the heart itself. The interior of the tumour contained several layers of coagulated blood, very dense and exactly like those found in aneurysms of the limbs—the tumour of the cavity communicated with the ventricle by a small opening, smooth and polished."

Hasse[6] reported that aneurysms of the heart were almost always restricted to the left side and was deeply puzzled by it. He also observed that the male sex had the greater incidence of these lesions as thirty-

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five of forty-seven cases cited were male. He further mentioned that aneurysms proved fatal "amid the usual symptoms of heart disease" implying that the usual mode of death was in congestive failure.

In 1843 Aran[7] noted that aneurysmal sacs were generally strengthened by partial and complete adhesions and that partial dilatation of the heart may last for "a series of years" without affecting the individual. He remarked that termination by rupture was most rare.

Extensive studies on the subject of cardiac aneurysm have been made by Hall,[8] Sternberg[9] and Parkinson et al.[10] More recently Berk,[11] Fulton,[12] Crawford,[2] Ball,[13] Dressler and Pfeiffer,[14] and Sigler and Schneider[15] have reviewed the subject and added to the clinical picture of the disorder.

Pathology: Occlusion of the descending branch of the left coronary artery, with resulting aneurysm of the apex or anterior surface of the left ventricle, represents the underlying pathologic feature in the majority of cases. The apex, farthest from the adequate blood supply, suffers most from the ischemic process. In the combined series of Schwedel and Gross[1] forty-eight of forty-nine cases showed involvement of the anterior or lateral portion of the apex of the left ventricle. Applebaum and Nicholson[17] found fifty-six of fifty-seven aneurysms located in the left ventricle.

Infrequent causes of cardiac aneurysms are trauma and congenital heart disease. Abscesses in the heart muscle which follow infective endocarditis have been mentioned as an etiologic factor. Gummas of the heart and rheumatic necrosis of the myocardium are found on rare occasions as precursors of aneurysms.

Scar tissue usually constitutes the wall of the aneurysm although muscle is occasionally present. Calcification of the clot or of the aneurysmal wall may occur. In Bean's series extensive calcification of the myocardial scars was found in three cases. Calcification of the cardiac aneurysm has been described as being more often linear and even, in contrast to pericardial calcifications which are more inclined to be thicker and irregular, such as seen in constrictive pericarditis.

It has been stated that bulges may be prevented from occurring by epicardial thickening or pericardial adhesions. In a review of eighty-one cases Schwedel and Gross found pericardial adhesions in nineteen patients while approximately one-half of the cases of ventricular aneurysms in Bean's[18] series showed pericardial adhesions. Ventricular thrombi may act as deterrents in preventing aneurysms. Smaller infarcts are less likely to produce this lesion. Increased intraventricular pressure should theoretically favor aneurysmal formation following myocardial infarctions.

Clinical Features. Shookhoff and Douglas[19] reported a case of aneurysm occurring within a week following coronary occlusion. On the other hand, bulges may not develop until seven years following an infarction. In the series of Parkinson et al.[10] the average duration of time between the attack of coronary thrombosis and the development of the aneurysm was seventeen and a half months. It has been emphasized by many authors that aneurysms are apt to occur in patients who have had inadequate rest or in those patients who undergo strain following infarctions. Sutton and Davis[20] have shown that dogs exercised three days following ligation of the left, descending coronary artery developed aneurysms in contrast to control dogs allowed to rest six days following operation. The control dogs had well healed scars and did not develop ventricular bulges. The following table indicates the

Author	No. of Cases	No. of Aneurysms	Per cent
Betsch[21]	141	11	8
Bean[18]	300	31	10
Applebaum and Nicholson[17]	150	57	38
Lisa and Ring[22]	100	5	5
Levine[23]	46	3	7
Parkinson and Bedford[10]	83	5	6
Wolff and White[24]	19	3	6
Wang, Bland and White[29]	528	52	10

reported incidence of ventricular aneurysm following occlusive vascular disease and myocardial infarctions.

In 7,200 autopsies Betsch[21] reports 1.5 cases of ventricular aneurysm per 1,000 cases which is in accord with the series of Lucke[25] and Rea who found 1.1 per 1,000 in 12,000 autopsies. The incidence of correct diagnosis by physical means varies with different investigators but it is evident that more cases are being recognized as attention is being directed toward antemortem diagnosis.

As Levine[23] and others have pointed out, coronary thrombosis is more commonly found in the male sex. In his series there were 111 males and thirty-four females a ratio of 3.5:1. In Mallory's[16] series 74 per cent of the patients with myocardial infarctions were males and 26 per cent were females. There is general agreement that approximately two-thirds of the cases of cardiac aneurysms occur in the male sex. This is undoubtedly due to the high incidence of myocardial infarctions in males.

In Parkinson's[10] study the average age of those developing ventricular aneurysm was fifty-six, the age limits being thirty to seventy-four.

A pulsation separate and distinct from the apical pulsation, especially when situated above the fifth rib, has been stressed by Libman[28] and others as a valuable sign. A visible and palpable apex impulse well within the outer border of dullness is pointed out by Levine[29] as helpful in diagnosis. In addition to the apical beat there may be the heaving impulse of the aneurysm or the aneurysmal thrust may be slight and quite difficult to detect on physical examination. A wavy pulse over the aneurysm has also been described. Libman[28] has stated that gallop rhythm in association with a dull first sound, together with pulsation separate from that of the apex, is pathognomonic of cardiac aneurysm. However, gallop rhythm was not noted in the cases of Crawford[2] or Dressler and Pfeiffer.[14] Many authors have stressed the disproportion between the faintness of the sounds and the impulse thrust.

Pain over the apex has been stressed by Lutembacher as of value in diagnosis.[30] In one of Crawford's[2] series this symptom was prominent. Localized precordial tenderness was found in 12.5 per cent of Berk's[11] series. Fulton[12] cites two cases of cardiac aneurysm with prolonged episodes of precordial pain following myocardial infarction.

Immobilization of the apex has been noted by Lutembacher.[30] Change of position from the right to the left lateral decubitus will occasionally demonstrate this immobility.

Cardiac decomposition, abrupt in appearance and difficult to control, is commonly found in these patients.

Most authors agree that there are no characteristic murmurs caused by cardiac aneurysm. Parkinson et al.,[10] Berk,[11] Crawford[2] and Ball[13] all noted the occurrence of apical systolic murmurs and Parkinson[10] refers to the work of Remlinger (1900), Straunch (1900) and Scherf and Erlsbacher (1934) who believed that a systolic and diastolic murmur over the aneurysm were suggestive in diagnosis. Tice[31] mentions the importance of a systolic murmur which suddenly appears following a myocardial infarction as being an important sign. In the series of Dressler and Pfeiffer[14] no murmurs were heard.

Radiologic Features. There is unanimity of opinion that roentgenograms and roentgenoscopy are most important in establishing the diagnosis. Oblique positions as well as the anteroposterior should be utilized. Aneurysms developing on the diaphragmatic surface may be difficult to detect. Schwedel and Gross[1] stress the aid of deep inspiration in visualizing the bulges occurring on the diaphragmatic surface. Parkinson et al.[10] suggest inflating the stomach with effervescent drinks as an aid in detecting apical bulges. Helpful diagnostic criteria are the presence of angulations, incisura, calcifications, increases in density, pericardial adhesions and bulgings.

The greater incidence of the diffuse type of aneurysms over the circumscribed bulging has been stressed by many authors. Commonly seen on x-ray are blunting of the apex or ledging of the anterior border. Often there is a sharp angulation of the left border giving the heart a square or rectangular appearance. Occasionally grooving of the left ventricular border occurs.

Pulsations because of their marked variability are cited by Schwedel and Gross as being not suitable for diagnostic criteria since they must be either "strong, synchronous, asynchronous, systolic or contrapulsile." Mural thrombi, pericardial adhesions and thickening may serve to modify the radiologic picture. Berk[11] cites the case of Christian and Frick in whom the hypertrophic muscle adjacent to the aneurysm was mistaken for the aneurysm itself. Displacement of the barium-filled esophagus may be of aid in some cases. Wolferth[32] et al. reported a case of obstruction to barium at the lower one-third of the esophagus due to aneurysm. Dressler and Pfeiffer[14] noted that in five of seven cases the lower one-third of the esophagus in the ROA position showed an impression from in front and also a dorsal displacement. There was no evidence of failure in these patients.

As pointed out by Parkinson et al.[10] an enlarged conus or dilated pulmonary artery may simulate aneurysms. Rotation of the patient will serve to differentiate aneurysms of the descending aorta which project to the left. Calcified pericardium may at times be confused with ventricular bulges but the linear shadow of the calcification and the distribution near the apex serve to differentiate these disorders. Tumors of the chest, periapical fat pads present in patients suffering with myocardial infarction, locculated pericardial effusions, coronary artery aneurysms, pericardial cysts and sinus of Valsalva aneurysms have been mentioned as occasionally simulating myocardial bulges.

Electrocardiographic Findings. Sigler and Schneider[15] as well as Crawford[2] do not believe there is any specific diagnostic value in the electrocardiograph in detecting cardiac bulges. Dressler and Pfeiffer[14] reported a deep S deflection in Leads II and III which are noted in one-half of the cases. Eliaser and Konigsberg[35] found in over a fourth of the patients in their series a downward directed major deflection in Lead I with inversion of the T wave and an upright P wave. Another type occurred in over a third of their cases characterized by downward ventricular complexes in Leads II and III, with an upright deflection in Lead I, that may or may not be of low amplitude. In 18 per cent of their series the electrocardiograph showed bundle branch block. Goldberger[34] pointed out that the aneurysm may cause unusual rotation of the heart, and when this occurs, there may be found a small R wave in Lead I and large S waves in Leads II and III; or the downward deflection of the QRS complexes in the three standard leads may be found. In his series all cases of ventricular aneurysm showed an upward QRS complex in the right arm lead which suggested to him that the absence of this pattern in the right arm lead of myocardial infarction would seem to rule out ventricular aneurysm. A deep Q wave in Lead I has also been mentioned as suggestive of ventricular aneurysm.[35] Although more or less persistent RS-T displacement does sometimes occur with myocardial infarction, its greater frequency in ventricular aneurysm is cited by Wilson et al.[37,38] and Theon.[36]

REVIEW OF CASES

Twenty-six cases of cardiac aneurysm proven by autopsy are reviewed in our series. Of this number twenty were admitted to the Cincinnati General Hospital from the years 1940 to 1948. Five of the cases were patients at the Jewish Hospital and one member of the group was admitted to the Christian Holmes Hospital, Cincinnati.

Age and Sex. The age range was from forty-five to eighty-six. At the time of death the average age was 65.8 years. Five of the patients were eighty years of age or older, their ages being eighty, eighty-one, eighty-

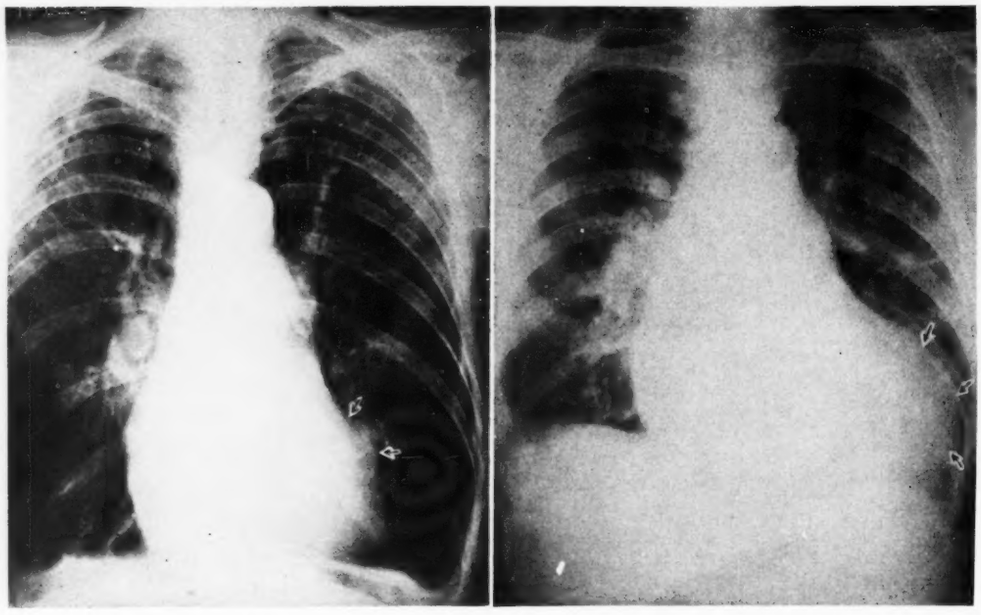

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FIG. 1. Illustration showing gross enlargement of the heart to the left, with blunting of the apex, resulting from diffuse type of aneurysm; necropsy confirmed presence of aneurysm.
FIG. 2. Teleoroentgenogram showing a circumscribed aneurysm of the left ventricle; necropsy confirmed presence of the aneurysm.

three, eighty-five and eighty-six. Four in the group over eighty years of age were males and one was female. The average age of males at the time of death was 64.5 years; the average age of females at death was 71.2 years. The youngest male was forty-five years of age and the youngest female was sixty-one years of age. Eighteen of the group were males and eight were females.

Pathology. Included in this series of twenty-six cases were only those patients in whom the cardiac aneurysm was proven by postmortem examination and in whom there were well defined cardiac bulges or sacculations. (Figs. 1 to 7.)

Of the 192 9.4 per cent consecutive myocardial infarctions at Cincinnati General Hospital studied showed ventricular aneurysms. In twenty-four of the patients an aneurysm involving the apex of the left ventricle was present; in two of the patients aneurysms of the septum were found.

In twenty-three of twenty-four patients with ventricular aneurysm old occlusions or atheromas in the descending branch of the left coronary artery were found. In one patient a thrombus was found occluding the left circumflex branch with posterior myocardial infarction and resulting aneurysm of the posterior wall of the left ventricle. In another case there was an old thrombus of the left descending branch and also a recent right coronary artery thrombosis. In one patient there were occlusions old and recent of the left descending artery, the left circumflex and right coronary arteries. (Figs. 5, 6 and 7.)

In three patients calcifications were found in the fibrous tissue of the myocardium, septum or pericardium. Nine had mural thrombi. Pericardial adhesions were present in approximately one-half of the cases reviewed.

There was no constant relation between the thickness of the ventricular wall and the occurrence of an aneurysm. Cases showing a thickness of 1 mm. sometimes did not exhibit a sacculation. One patient had a 4 cm. dilatation of the ventricular septum. There was extensive myocardial fibrosis and the arteries were soft and patent. The etiology of this aneurysm was undetermined. An aneurysmal dilatation of the septum membranaceum was found in one patient.

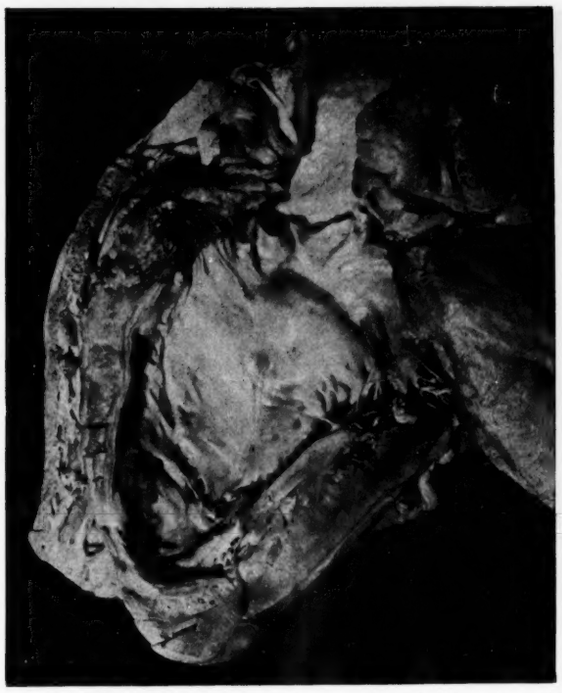

FIG. 3. Marked thinning and aneurysmal dilatation of the left ventricular wall at the apex.

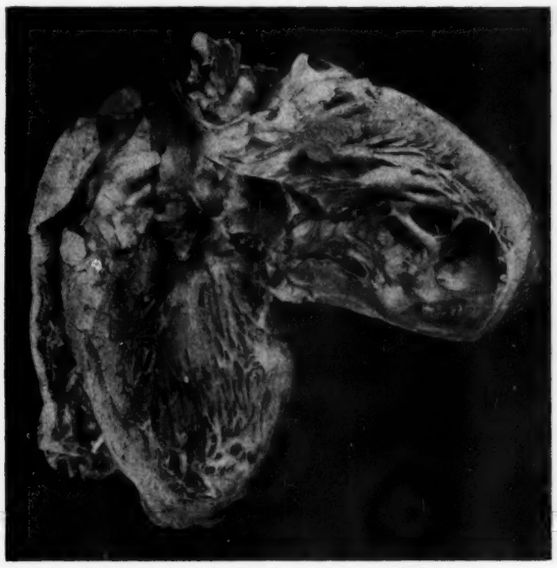

FIG. 4. Aneurysmal dilatation of left ventricle, following coronary thrombosis, left circumflex artery and posterior myocardial infarction; patient developed a blowing systolic murmur on the ninth day following coronary occlusion and at that time the possibility of perforated interventricular septum (or ruptured valvular cusp) was entertained.

The ostium measured 2 cm. in diameter with a depth of 1 cm. This aneurysm was of congenital origin.

Clinical Features. The features which occurred most often were the following: low blood pressure or normal blood pressure (91.6 per cent), cardiac enlargement (79.1 per cent), history of coronary occlusion (75.0 per cent), distant or weak heart sounds or a weak first sound (50.0 per cent), persistence of congestive failure after the onset of failure following myocardial infarctions (37.0 per cent), visible and palpable apex beat within the outer border of dullness (25.0 per cent), an impulse separate from that of the apical thrust (16.6 per cent), having precordial thrust (12.5 per cent) and disproportion between the precordial thrust and weak heart sounds (12.5 per cent).

A rough systolic murmur suddenly appeared following a myocardial infarction in one case, localized precordial tenderness appeared in one patient and a to-and-fro murmur over the apex was also present in one patient.

In twenty-two patients the blood pressures were normal or subnormal. In one patient the blood pressure was 200/130 and in another the blood pressure was recorded as 200/100. These pressures were unusual in the series.

Cardiac enlargement was noted in nineteen patients and on percussion the left border of cardiac dullness was frequently described as extending to the anterior axillary line.

A history interpreted as a past coronary occlusion was obtained in seventeen cases. Frequently a history of neglected treatment and abbreviated period of bed rest was recorded; on the other hand, one of the patients with very satisfactory treatment developed the aneurysm while under observation.

Twelve of the patients had weak or distant heart sounds and in this group three had a distant first sound. In ten patients a systolic murmur was heard which varied in quality and intensity, being described as rough, soft, loud, blowing or grating. In one patient there was a sudden appearance of a rough, loud, systolic murmur within the apex nine days following myocardial in-

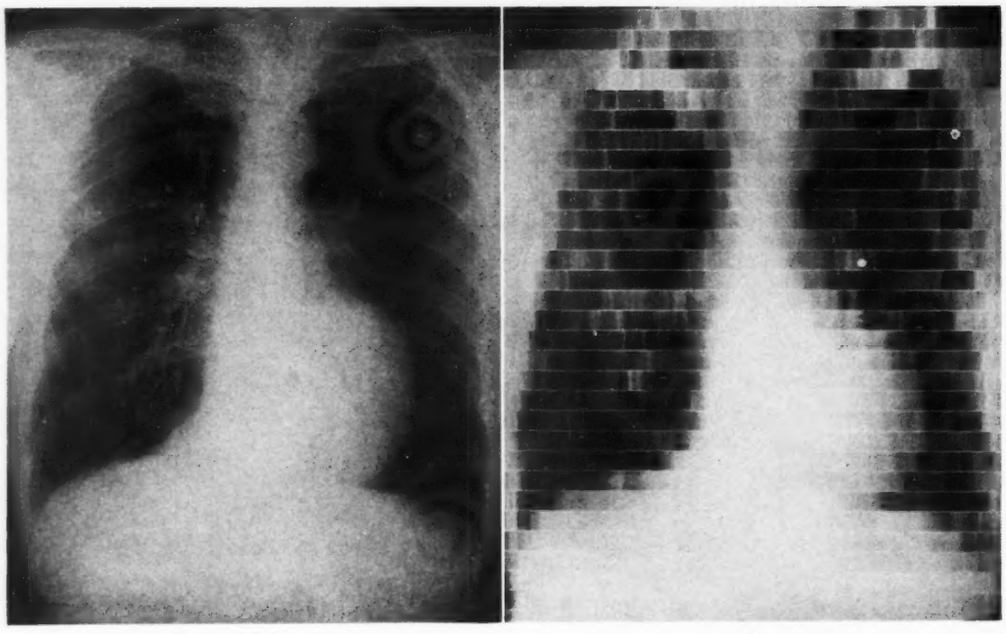

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FIG. 5. Teleoroentgenogram showing aneurysmal dilatation of the left ventricle and "squaring" of the heart; autopsy confirmed the presence of ventricular aneurysm which was present for seventeen years.

FIG. 6. Kymograph of the patient in Figure 5; roentgenograph and kymograph do not reveal the true extent of calcification of the left ventricle which measured 8 or 9 cm. in the greatest diameter.

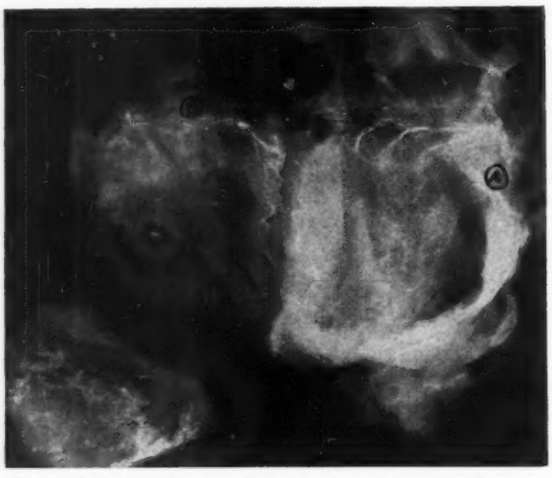

FIG. 7. Injected heart of the patient shown in Figures 5 and 6; the left ventricle is shown on the right, the right ventricle on the left side of the photograph. Septum shown in the lower left corner. A, old occlusion of the left descending anterior artery 2½ cm. from its origin; B, recent occlusion of the left circumflex and evidence of occlusion of the branch of the right coronary artery. Marked deposit of calcium throughout the left ventricular wall and septum and increased anastomoses in right ventricular wall.

farction. This murmur varied in intensity, often heard best near the apex, occasionally loudest in the third or fourth interspace about 1 cm. to the left of the sternum. This patient was first suspected of having developed a perforated interventricular septum or a ruptured cusp. In one patient a to-and-fro murmur was heard over the apex, this being the only patient presenting a double murmur over the aneurysm.

Persistent congestive failure was present in nine of the patients. Once failure occurred there was difficulty in maintaining cardiac compensation despite adequate therapy.

In six cases a visible and palpable impulse was recorded within the outer border of cardiac dullness. An impulse separate from that of the apical beat was found in four patients. Three of the cases demonstrated a heaving precordial thrust and in these patients there was a disproportion between the precordial thrust and the weak heart sounds.

No alteration of cardiac rhythm could be noted which would be of diagnostic significance. One patient had paroxysmal ventricular tachycardia and three patients showed auricular fibrillation. There were three patients with gallop rhythm.

No history of dysphagia was found in any of the patients and there were no symptoms attributable to the aneurysm, with the exception of one case. This patient complained of more or less constant pain over the apex. Congestive failure difficult to control was present in this same patient.

No correlation between age and sex could be drawn as predisposing factors.

There was no electrocardiographic picture which could be termed diagnostic of ventricular aneurysm although suggestive features were observed. A deep S wave in Leads II and III was frequently observed in nine patients. The upward QRS complex in the right arm lead was found in two of three cases. Seven of the patients showed persistent displacement of the ST-T segments. Left bundle branch block was found in three patients.

Prognosis and Mode of Death. It is surprising how little incapacity some patients suffered despite the presence of aneurysm. One of the patients died ten days following the onset of a coronary occlusion. At the other extreme, another patient survived seventeen years after the diagnosis of ventricular aneurysm was established. (Figs. 8, 9 and 10.)

All patients with the exception of one died in congestive failure. One died with emboli to the brain, spleen and kidney. The death of another patient was presumably due to a combination of emboli and congestive failure. In no case did cardiac rupture occur.

COMMENTS

In the Cincinnati General Hospital series 9.4 per cent of patients with myocardial infarction developed ventricular aneurysm. This estimate may be somewhat conservative since only the well defined sacculations are included. There were questionable cases reviewed which could have been regarded as aneurysms thus increasing the average considerably.

The average age of the twenty-six members of the group was 65.8 years.

The frequency of mural thrombi and pericardial adhesions was high, which is consistent with other published reports. Approximately one-half of the cases showed pericardial adhesions while mural thrombi were present in one-half of the patients.

Many ventricular aneurysms were discovered for the first time at autopsy. This might be due to the short period of observation in some of the patients.

It seems apparent that if one expects to find all the classic signs of ventricular aneurysm, the clinical diagnosis will be missed in some of the cases. It should be borne in mind that the less frequent features are sometimes important in suggesting the diagnosis.

In the majority of patients correctly diagnosed antemortem the diagnosis was first suggested by the radiologic examination. This may be because (1) the possibility of aneurysm was not kept in mind frequently enough or (2) the physical signs of aneurysm were not always present.

SUMMARY

The literature on cardiac aneurysm and twenty-six additional cases proven by postmortem examination are reviewed.

In 192 cases of consecutive myocardial infarctions studied at autopsy at the Cincinnati General Hospital ventricular aneurysms were found in eighteen patients. (9.4 per cent.) In the majority of the cases correctly diagnosed antemortem the diagnosis was first suggested by radiologic examination.

There was involvement of the apical portion of the left ventricle in the largest group of the cases, with the aneurysm appearing on the anterior wall. This aneurysm commonly followed occlusion of the anterior descending branch of the left coronary artery.

Features helpful in making the diagnosis are: a history of coronary occlusion, normal or low blood pressure, cardiac enlargement, distant or weak heart sounds or a weak first sound, persistence of congestive failure after the onset of failure following a myocardial infarction, visible and palpable apex beat within the outer border of

cardiac dullness, heaving precordial thrust, cardiac impulse separate from that of the apical impulse and disproportion between the heart sounds and the precordial thrust. Pain over the apex, a to-and-fro murmur heard over the apex and immobilization of the apex are also suggestive in directing attention to the diagnosis. A rough, loud, systolic murmur occurring suddenly following myocardial infarction should arouse suspicion as to the possible presence of an aneurysm, in addition to the possibility of a perforated septum, rupture of valvular cusp or chorda tendineae.

No pathognomonic electrocardiographic changes were found in the twenty-six cases studied.

Prognosis in this series was quite favorable. A patient is reported who survived seventeen years following the development of a ventricular aneurysm.

Death was commonly due to congestive failure. Rupture of a ventricular aneurysm did not occur in this series.

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Seminars on Cancer Research

Neoplastic Infection and Cancer*

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If, despite the variety of its manifestations, one thinks of the profound morphologic and functional unity of malignant disease and of what cause could reasonably explain all the features of malignant disease, it would seem that one should reason as follows: (1) Since cancer is characterized by the indefinite growth of cells, the cause must need these cells and multiply along with them. (2) Since cancer develops as a result of the most varied stimuli and in the proper background, the cause exerts its effects only in ground properly prepared and in the right genetic environment. (3) Since cancer, on the one hand, develops with great frequency in selective tissues but may occur in many of them, the cause must be highly specific yet must also have the property of almost infinite variation. (4) Since cancer attains its highest incidence in maturity and old age, the cause must either be capable of remaining latent in tissues for practically the whole life of the host or else find its optimum environment in a ground that age has changed. (5) Since tumor preparations free of cells can reproduce the disease in some types of cancer but not in others, the cause must be endowed with the power of manifesting itself either in a free or occult, state, both states being interchangeable.

The title of this paper has already indicated one conclusion that can be drawn as to the nature of this cause. For, with regard to the first of the requirements previously listed, it is superfluous to point out the fundamental parasitic nature of the viruses, their power in many cases to stimulate cells to grow before destroying them and to multiply at the same time that the cells multiply.

Observing the smooth gradualness in the steps from virus necrosis to virus neoplasia, one is not surprised to see that fowl pox virus causes the formation of large masses of epithelial cells, which may persist for several weeks, if one remembers that in the preceding step of the ladder vaccinia virus is found to cause comparable though less pronounced cell stimulation lasting only a few days or hours depending on the strain. Nor is one surprised, remembering the case of fowl pox, to see in the succeeding step that papilloma virus induces the formation of still larger masses of new cells which may persist for months or years.

Concerning the second requirement there is hardly any need to insist on the close conditioning of viral or any other infection by the genetic background and by certain conditions found in tissues altered by hormonal, chemical and many other means. Examples have been given elsewhere.[1–3] One point, however, is worth remembering, namely, that of the excellent ground offered by embryonal cells, or even cells from newborns, for the growth of viruses as attested by the easy growth of dozens of them in embryos or media containing embryonic tissues.

Regarding the third requirement we have to examine together two well known properties of viruses, their specificity for this or that cell or tissue and their capacity

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to vary. The characteristics of virus lesions are monotonously repetitious provided the environmental conditions remain constant. Yet, one of the properties that a virus acquires after variation, brought out by so many means but especially by change of species, is that of attacking cells or tissues not affected by the original strain. Thus we speak of neurotropic, viscerotropic, pneumotropic, dermotropic variants of so many viruses. Therefore, *specificity* and *variability* are, as it were, antagonistic to each other. The former property insures constancy of lesions; the second, variety more or less pronounced depending on the inherent capacity of the virus to remain or not to remain constant.

As for the fourth requirement, we must remember the basic property of some viruses, and of so many other infectious agents, of remaining latent in tissues after overt or subclinical infection, an event closely related to the immunity that follows. Moreover, increasing evidence indicates the frequency with which viruses can invade hosts, from the dawn of postembryonal and even embryonal life, and persist in the host until death without any sign of infection. Casual findings, mostly in mice, are largely responsible for this knowledge, the best examples that can be quoted perhaps being those of choriomeningitis, mouse poliomyelitis and salivary gland viruses.

As for modification of viral infection by the age of the host, the following can be said: Studies on the relation of age to infection are numerous,[4] all of them establishing experimentally the fact, long recognized from clinical observation, of the greater susceptibility of the young to most infections. However, what so far has not been studied but may constitute a novel approach to infection, especially chronic infection, is a fact that seems to emerge from recent observations, namely, that *infection of the old and generally more resistant host may manifest itself preferentially by cell proliferation rather than by cell destruction.* This is precisely one of the main phenomena around which our own work on tumor viruses turns. The best evidence illustrating the point will be discussed later. In the field of non-neoplastic ordinary viruses we can quote among others the following examples, some very instructive, of what could well be termed *neoplastic* infection as opposed to *destructive* infection.*

1. Sheep pox and allied viruses induce in the young essentially destructive pustular lesions in a disease pattern which is often lethal, whereas in the adult they induce typical mild papillomas.[5,6] The identity of these lesions in the adult cannot be clearly established unless one resorts to passing them to young hosts which react with typical pox.[6]

2. Infection of the chick embryo by herpes virus is proliferative and but little necrotic in the late stages of development, the opposite being true in early stages.[7]

If one enters the domain of viruses so proliferative in their effects that they are often discussed in relation to cancer, the facts are even more enlightening, especially in the case of fibroma virus.

1. Myxoma virus is far less proliferative and more destructive in young than in old animals.[8,9]

2. Fibroma virus inoculated in large amounts into newborn rabbits causes an acute, lethal disease with traits largely destructive and inflammatory. When injected in small amounts, or after storage, it induces progressively growing tumors, sometimes very large, which either regress leaving the animal immune or can in their turn generate satellite nodules and generalized fibromas, to all intents and purposes metastases. Virus secured either from the necrotizing or the tumorous lesions induces in the adult the usual mild fibromas which always regress leaving the rabbit immune.[10]

This duality of effects of viruses or other infectious agents has also been observed in cases not directly correlated with age as the following:

Sheep dermatitis virus induces pustular, degenerative lesions in the guinea pig whereas in the rabbit it induces very proliferative, papil-

* In this review we shall use the expression neoplastic infection as a convenient term denoting that some sort of cell proliferation is induced by some infectious agents. Such lesions would be called hyperplastic or just proliferative by pathologists.

loma-like lesions.[11] Attenuated myxoma virus induces lesions in rabbits far more proliferative than fresh, active virus.[12] Fibroma virus can manifest itself either as inflammatory or as proliferative through changes in the virus suggesting mutation.[13] Bartonella bacilliformis, cause of the acute, often lethal Oroya fever, is followed on recovery by a real fibro-angiomatous tumor, verruga peruviana.[1]

The fifth requirement takes us to a brief review of an ensemble of possibly disconnected phenomena which, at least for the time being, are considered under the loose designation of "masking," a term denoting the situation in which a virus may be present in an infected tissue or cell and yet is not demonstrable by current methods. As in the phenomena dealt with in the foregoing section, perhaps the most outstanding evidence of masking is to be found in the domain of cancer viruses, but we shall endeavor to gather the evidence available from ordinary virus infection which may serve as a basis for further and more comprehensive study of this important subject.

In orthodox bacteriology as far as we know when a tissue remains negative after microscopic study, cultures or animal inoculation, one considers that bacteria are absent. However, this is not the case with at least several viruses, as shown by the fact that the virus can be demonstrated in the tissue either by direct "unmasking" means or by indirect methods. A tentative grouping of known cases follows:

1. A variety of neurotropic viruses, after having exerted their effects on the central nervous system, cannot be transmitted by inoculation of the ground tissue to other hosts. These cases were designated by Levaditi as "self-sterilizable neuro infections." The intransmissibility of the protracted herpes infection in rabbits described by Perdrau probably falls in the same category. At least in the last infection the virus can be unmasked by storage in glycerol, by electrophoresis and by dilution of the extract.[14–16]

2. Virus could not be demonstrated under some circumstances in extracts of viscera from chickens infected with the virus of avian pest or in extracts of rabbits recovering from vaccinial infection. In the last case the virus was unmasked by electrophoresis or by repeated passages.[14–16]

3. Salivary gland virus of some strains of mice induces a rapid lethal infection when injected intraperitoneally. Extensive lesions with typical inclusion bodies are found in the liver and other viscera; yet injection of the extracts of these tissues consistently fails to reproduce these lesions in other mice.[17]

4. The virus of swine influenza carried by the hog lung worm does not become infectious unless the provocative stimulus of H. influenza is at play.[18]

5. In virus infection of plants the virus of the sour cherry tree together with other viruses of the group can be transmitted only by grafting of the infected tissues and not by direct inoculation of healthy plants with juice of the infected ones. However, transmission by this method can be accomplished if extracts from young leaves of the cherry tree are inoculated into young leaves of cucumber.[19] An analogous situation is found in the case of the wound tumor virus which is only transmissible when previously passed to leaf hoppers.[20]

6. In bacterial viruses infection of the bacterial cell by bacteriophages radiated with ultraviolet light is possible only when more than one phage particle is at work. Reconstruction by so-called genetic recombination is indispensable.[21] Therefore, there is a stage in which an isolated particle, evidently altered or damaged, is only potentially active and can be made actually active, that is unmasked, by an effect from another phage particle.

Because the unmasking effects are so varied, one may judge the masking phenomenon as being extremely complex and heterogenous. However, from the conditions leading to masking itself or from those leading to unmasking, one can surmise that masking may be the result of the following: (1) an antigen-antibody combination which can be broken by dilution of the tissue extract or possibly by other means (herpes and possibly other viruses); (2) an effect from a factor present in tissues other than those naturally affected by the virus in the same host (salivary gland virus); (3) a more complex effect involving, among others, infection of a vector species, the effect being suppressed by the action of a bacterial factor (swine influenza); (4) an effect from a factor present in the tissues

of the commonly infected host which is suppressed by passage to other and sometimes extremely remote hosts (plant viruses) and (5) an effect from a physical agent which is compensated for by a conjugation-like event (bacteriophages).

We do not know whether common denominators could be found in a number of these effects, thus giving more unity to the masking phenomenon. One sees masking closely linked with other phenomena of basic importance in host-parasite relations. Thus the persistence of immunity in convalescent hosts attributed to the virus remaining latent may be put side by side with masking, whereas the recovery and reactivation of this virus by the old Pasteur method of animal passage could be identified in some ways with the process of unmasking.

Masking may well play a part in experiments in which influenza virus after becoming adapted to grow in eggs induces lesions in the original host (the mouse) in the first passage but only with great difficulty upon further passages until the virus is completely readapted.[22]

From the reconstruction of an active bacteriophage by merging of inactive phage particles one is led, on the one hand, to the broad field of photoreactivation after inactivation by ultraviolet light and, on the other hand, to the reactivation of heat-inactivated myxoma virus by the effect of an intact fibroma virus (Berry-Dietrich phenomenon). The freeing of masked viruses by transfer to other hosts may be of great importance, especially if one thinks that at least in one case an insect vector is responsible for the phenomenon.

* * *

It is not easy to know what is the reaction of people to the so-called "virus theory of cancer," the theory that all or most cases of cancer are manifestations of virus infection. Judging by what is written it is far from popular, but the opinion of people who think and do not write is just as good as the opinion of people who think and do write. The theory may also be favored by workers who write on viruses but not on cancer. On the other hand, it seems to us that some workers in the field of cancer viruses are mainly concerned with a particular type of tumor associated with a known causative agent which may not even be considered a true virus or the real, immediate cause of the tumor.[23]

It would seem, indeed, that the so-called endogeneous theories are favored by most cancer workers. The number of these theories is endless and frequently repeat in different words views that one finds in old textbooks, rejuvenated by fresh findings.

One thing, however, is common to all these theories, namely, that after the cause or carcinogen has induced a sudden or gradual change, preferentially in specially receptive cells or cells of an embryonal type, either directly or by removing an inhibitor, these cells multiply endlessly as if victims of a strange biologic inertia. What impulse causes the cells to multiply after the initial stimulus has long disappeared is to be found only in intrinsic forces of the cell itself. As a result of this process the cell develops the properties of malignancy that we all accept and, incidentally, have so often been confused with the cause of this malignancy. Its profoundly changed metabolic pattern in which the growth-stimulating forces predominate allows this "anarchic" or "autonomous" cell to invade not only the host in which it originated but also hosts from foreign species, thus overcoming genetic barriers. The cancer cell has been considered then to have lost its species identity and to behave as an embryonal cell.

The plausibility of this phenomenon is enhanced by analogy with a somewhat similar situation, the change of a bacterium from an avirulent to virulent form. Here, too, a change in the bacterium, often sudden, allows it to multiply in surroundings utterly adverse before the change took place. Thus virulence and malignancy would be interchangeable terms.

The supporter of the virus theory (let us call him the virologist) must admit that the

analogies between bacterial virulence and cell malignancy constitute perhaps the most powerful argument in favor of the endogenous theories, especially if two additional concepts are added. The first is that in the same way that bacterial variants appear in an adverse medium, old cultures or recovering hosts, so, too, could cell variants appear in a medium made adverse by a variety of agents, including aging. The second is that just as bacterial types varying from avirulent to virulent are induced by chemical compounds detachable from the bacterial cell itself,[24] and are indefinitely transmissible in the new type, so could similar endocellular products induce the change from a normal to malignant cell.

However, the virologist can argue against this interpretation of the aforementioned facts and his views could be thus summarized. Although the analogies between virulence and malignancy are undeniable, comparable results can be produced by entirely different causes. Even at the risk of getting a bit metaphysical, the transforming bacterial principles, as far as we know, must be considered as reverting an imperfect, degenerate cell to its normal, perfect form, that is the opposite of the cancer cell universally accepted as an aberration. Less metaphysically and more philosophically, the virologist can postulate that a medium made adverse, although possibly conducive to cell mutation, may also be ideal for such highly conditional entities as viruses. And, if cell mutation, were to occur preferentially in especially receptive or in embryonal cells, the subtle specificity of viruses and their great ability to thrive in embryonal cells or tissues can well be brought up. Finally, with no recourse whatsoever to metaphysics or philosophy, the virologist can show how agents generally accepted as exogenous viruses, such as pox viruses, herpes, etc., will induce cell hyperplasia, of more or less limited duration it is true, which could mystify any pathologist caught unawares.

To all this the follower of endogenous theories (let us call him the mutationist) would object, first that metaphysically the cancer cell, far from being an aberration, could be considered just as perfect as the smooth pneumococcus; having reverted to an ancestral type, autonomous, self-supporting and, no doubt, more powerful than a normal cell. He may admit that an adverse medium may favor the action of viruses and that such viruses induce transitory cell proliferation which, however, can in no way be compared to cancer growth since comparable pseudomalignant changes can be seen after injection of certain dyes[2] and talc powder[25] or following insect bites.[26]

To the latter the virologist would retort by saying that if the component of the insect poison or the granules of dye were endowed with the power of multiplying, as are viruses, the process would eventually lead to one identical with cancer. Moreover, can phenomena taking place in unicellular organisms be closely compared to those taking place in pluricellular ones? For, as pertinently stated by Rous, the changes in tissues known as somatic mutation never result in proliferative phenomena, and tissues are after all our real subject matter.

By definition we know that the virologist would never convince the mutationist, and vice versa. Evidently, the specialized worker suffers from some professional deformity with a touch of professional vanity, that makes him look at the agents and phenomena with which he is so familiar as capable of accomplishing what is inconceivable to another specialist equally deformed by his knowledge.

Attempting to summarize these speculations, one could perhaps state the following: There is unanimity among workers in that cancer is the result of a sudden, more or less pronounced change or succession of changes. For the mutationist this change is the disease itself; for the virologist the change prepares the ground for a virus effect. For the mutationist, therefore, cancer is an event, a perversion, a disease of inheritance and growth, and if so the possibility of finding means to prevent it is exceedingly

remote. For the virologist cancer is a highly conditioned manifestation of viral infection which, if perfectly understood, could be prevented just like any ordinary infection. And to support this last statement the virologist has an important fact, purposely disregarded by us in the preceding theoretical polemic but which we shall now fully discuss, namely, that quite a variety of cancers *are* produced by viruses.

In practically all the animal species in which cancer has been thoroughly and systematically studied a number of these cancers have been found to be caused by viruses. The etiologic problem of these tumors has been entirely solved, and in view of the essential unity observed in all cancers it is elementary logic to look for the same etiology in growths of unknown cause.

What can be the position of the mutationist in the face of this fact? It would seem that there are only two courses to follow. The first is to accept explicitly the viral cause of these cancers, considering viruses as typical exogenous entities while reserving the mutation theory for the rest of tumors: Cancers of "known etiology" are the result of viruses about which we know something; cancers of "unknown etiology" are the result of mutations about which we know almost nothing. The second course would be to assume that viruses, at least those producing cancer, are normal cell components which through cell mutation into malignancy are transformable into autonomous agents, become incorporated into other cells to which they impart the power of mutating into malignancy; these cells in turn produce more such viral agents.[27]

This is certainly not the occasion to discuss so important and broad a subject as that of the origin of viruses. However, for our problem the following statements seem pertinent.

1. Data from sound epidemiologic investigation do not lend support to the idea that virus epidemics (or any other epidemic for that matter) appear in a haphazard way as the result of unpredictable mutations in components of normal cells. On the other hand, recent work has proved that lymphomatosis, a contagious neoplastic disease of chickens, can be suppressed by isolation.

2. Despite many attempts with bacteriophage, plant viruses and also tumors there is not the slightest indication that viruses, at least viruses orthodoxically accepted as such by virologists, can be obtained from normal cells by special treatments.[28]

3. There is no proof that tumor viruses are of a different nature from other viruses in that the former would be endogenous and the latter eoxgenous.[3]

In connection with these problems it is imperative to keep clearly in mind the basic fact that such subtle variations exist in host-parasite relationships as to result in various states, commensalism symbiosis, parasitism, which are often so well balanced as to lead one to confuse normal physiology and infection.[29,30]

Any attempt to elucidate the behavior of viruses would be impossible without always keeping in mind the concept of latent infection. This may be present both in the adult and in the embryo, examples of the latter being choriomeningitis, Newcastle disease and lymphomatosis and of the greatest importance in connection with the following facts, among others: (1) the experiments of Notre Dame which may supply us with material probably germ-free for the bacteriologist but perhaps not for the virologist; (2) the experiments on malignization of tissues, in artificial media, with or without carcinogens;[31,32] although not exactly comparable, one may consider, also, as possibly bearing on the subject those other experiments in which cells in tissue cultures became contaminated with sarcoma viruses. (Chapter on viruses[28]). (3) the experiments in which one seeks alterations in the normal incidence of carcinogenesis by transfer of ova from one strain of mice to others[33] and (4) the experiments on the rapid carcinogenesis obtained when mouse embryo tissues mixed with methylcholanthrene are grafted into mice.[34,35] The multiplicity of cancers obtained together with other considerations prompted two of the aforementioned[34] authors to conclude that a virus effect was absolutely excluded.*

* It is pertinent to quote some of our results in this connection. When in experiments parallel to those quoted above chicks were grafted in the breast muscle with a variety of embryonic homologous tissue powdered

To the virologist the carcinogen acts by making possible the action of a latent virus. We feel compelled to clarify the concept of latency in answer to the following statement of Boycott; "When it becomes necessary to postulate a normal virus occurring in normal cells, one had better call it something else than a virus." This is a supposition gratuitously attributed to the virologist which, so far as we know, no virologist has ever made.* As understood by the student of infection in general, latent infection is that involved in the *carrier* state in which the virus, free or masked, is present in this or that tissue or secretion—by no means in all cells.

Workers have turned to other fields to produce evidence in favor of the derivation of viruses from normal cells; functional, biochemical and even immunologic analogies between viruses and components of the nucleus or cytoplasm have been repeatedly emphasized.[36–38] Dealing with autonomous entities offering the characteristics recognized in living matter, it is logical to suppose that such analogies exist, but what does not seem so logical is that they may establish derivation of one entity from another. For instance, there is a duplication of components, complex enough to constitute antigens, between certain rickettsial agents and some bacteria of the Proteus group, both infectious agents being sometimes found in the same patient. No doubt this is a perplexing state of affairs that can be interpreted in several ways, one of them being perhaps to assume the existence of an ancestral form common to both agents. But can one accept the evidence as indicating that derivation is taking place daily as a matter of course, as postulated for every case of cancer or at least for every case of chicken tumor? The supposition becomes still more risky if applied to cells, animal and bacterial, containing the Forssman antigen.

On the other hand, an increasing amount of evidence shows that components of the infected tissue may appear as if part of the virus. In view of the very nature of these agents it is perhaps difficult to imagine a virus infecting a tissue without constituents of the latter being somehow incorporated in the former.

As for the principles operating in the transformation of pneumococcus, one may well reason that these principles, as far as we know, operate *within* a species whereas viruses are infectious agents and fundamentally *infection is the invasion of one species by another*. By the same token, neither can the autocatalytic transformation of, say, a row of molecules of trypsinogen into trypsin be compared to a virus effect. The transformation of the first molecule of trypsinogen can be carried by a molecule of trypsin from a different species, and no antigen from this species is found in the last molecules of trypsinogen changed.[28]

Although here again it is difficult to know what the opinion of workers is, one has the impression that the view that viruses and other infectious agents as well are degraded representatives of higher and more independent forms of life is gaining ground. The names of Green and Laitlaw are associated with this opinion. For some strange reason a similar theory of Charles Nicolle[30] is rarely mentioned. As we shall see later the notion of degradation as applied to viruses in general may be a fruitful one in cancer, for such a state occurs in a more advanced degree in some cancer viruses.

The analogies between the old polemics on spontaneous generation and those on the origin of viruses have been frequently pointed out. We would like to refer the

with methylcholanthrene, tumors rapidly developed in every case; but, curiously enough, these tumors were all sarcomas of the sort obtained when the carcinogen is injected directly into the same site. However, there is an important difference between the two kinds of tumors in that those developing after injection of embryo tissue and methylcholanthrene had a much greater capacity for indefinite transplantability than those developing after injection of even larger amounts of methylcholanthrene dissolved in various vehicles. Experiments under way will decide whether the difference is due to the presence of embryo tissue or to the greater concentration of the undissolved carcinogen in a limited area of tissue.

* It will be of interest in this connection to read a paper by Altenburgh[36] concerned with the "viroid" theory of cancer.

reader to a statement by Pasteur[39] concerning the first rabies virus and the first mad dog. It was a pasteurian, Borrel, who was the first to postulate, with uncommon insight, the virus theory of cancer.[28]

* * *

Among tumors induced by viruses one finds some in which the causative agent is as easy to demonstrate as in many ordinary viral infections.

Thus the papilloma virus of wild rabbits is easily transmissible to other wild rabbits by scarification with filtrates and is generally found in a free state in the growths thus induced.[40] Some naturally occurring chicken sarcomas yield filtrates from the first passage which induce tumors in the same heterozygous breed of chickens. Also, it has been found that in the course of further passages these viruses are active in most breeds of chickens.[41] Filtrates from adenocarcinoma of the leopard frog's kidney most probably transmit the disease to other leopard frogs, but only to them. The frequency of the naturally occurring disease complicates the results somewhat.[42]

In other cases the virus is more exacting and demands special conditions of genetic receptivity from the host.

Thus the viruses of some chicken sarcomas are not demonstrable until after several or many passages of the growth by cells.[41] The viruses of most strains of lymphomatosis and lymphocytomas are active only in strains of chickens specially bred for susceptibility to the disease.[43] Curiously enough the genetic factor can differtiate susceptibility to the virus from susceptibility to the cell. This is shown by experiments from our laboratory[9] in which many Plymouth Rock chicks were injected either with cells or filtrates of the lymphoid tumor RPL 12 (Olson tumor). The typical disease developed in almost every instance after cell inoculation whereas filtrates were ineffective. A similar state of affairs was suggested long ago from experiments in which fresh and desiccated sarcoma tissue was inoculated in the same fowl.[44] The virus of wild rabbit papilloma is active in domestic rabbits but to show its presence in the lesions produced one has to resort to special means such as inoculation in the skin prepared by carcinogen[45] or to concomitant infection with another virus.[46]

Finally, in other cases the virus requires, besides a distinct genetic background, special preparation of the host's tissue by estrogenic hormones which act in a mammer equivalent to aging of the individual. This applies, of course, to the virus of mammary gland cancer of mice.

It was in 1932[47] that Lacassagne discovered the important fact that inoculation of estrogenic hormones induces mammary gland cancer. Taken at its face value the finding appeared to be convincing proof in favor of the endogenous theories since a hormone which normally causes growth and differentiation of the mammary gland was shown to induce cancer when overdoing its mission. Yet, thanks to the work of the Jackson Memorial Laboratory, we now know that what the hormone does is just to prepare the ground for a virus present in the milk and other body fluids or tissues in the proper genetic background.

The virus of the mammary gland tumors of mice was discovered in the same way that Robert Koch could have discovered the cause of tuberculosis had he made healthy calves nurse from tubercular mothers, and vice versa. Thus the tubercle bacillus could well have been called a milk factor and so could Brucella melitensis or some streptococci for that matter. Yet the fact that an infectious agent is ordinarily found in the milk does not mean that it must always be found there, although present elsewhere, and thus one is surprised to note that some workers argue against a possible virus cause when they observe that the incidence of a given type of cancer is not changed by foster nursing.

The following recent investigations by von Magnus[48] are most timely in this connection. It is known that the virus of encephalomyelitis of mice (Theiler) appears in the intestinal tract shortly after birth to persist there for the duration of life. The Danish authors have succeeded in raising a colony of mice entirely free of virus by foster-nursing the newborn by rats, a species never harboring the virus. Further, paralleling events in breast tumors of mice or suggesting possibilities in the spread of the latter disease.

these mice can become infected later on by means other than suckling; they become carriers and transmit the virus to the progeny by nursing. This happened once unintentionally and in another case by purposely contaminating the cages with infected stools.

It may be concluded, therefore, that the greater the difficulties in showing the presence of a virus in tumors where one knows the virus to be, the more one should suspect a similar cause in other tumors.

* * *

Avian cancer is of special interest to us because here the infectious cause has been demonstrated in a large group of many different tumors. The incidence of naturally occurring cancer in chickens is one of the highest among animal species even if lymphomatosis is not included. The types of cancer often are the same as those found in other species including man and, excluding lymphomatosis, occur in comparable ages. Lymphoid tumors and leukoses account for about half the total percentage of malignancies. Excellent reviews have been published on classification, incidence and many other aspects of chicken tumor and leukosis.[49,50]

For our purpose we shall itemize avian malignancy from the standpoint of their virus etiology as follows: (1) several leukoses,[51] the viruses of which were discovered by Ellerman in 1909. A great deal of the interest of workers in these conditions has centered on topics of classification and derivation of the strains. The factors responsible for the differences of opinion in this field are: first, the great flexibility of the mesenchymal cells themselves, the genealogy of which has in turn provoked so much discussion, and second, the properties inherent in the causative viruses (variation) resulting in changes of specificity or in the formation of mixed strains (a state of affairs very reminiscent of what is observed in many groups of plant viruses) and which fully justifies the flexible term of "avian leukoses complex" applied to this group of diseases; (2) sarcomas of various sorts and endotheliomas, the virus cause of which was discovered in 1911 by Rous and Murphy of the Rockefeller Institute and by Fuginami[52,53] and (3) lymphoid tumors and lymphomatosis, the cause of which is today solidly established.[50] A further possible type is gliomas,[54] as indicated later.

As for epithelial tumors, especially prevalent in old age, we face the curious situation that except in very rare instances they are not transplantable by cells, thus depriving us of the most valuable means for study of their cause. Nevertheless, the following results could be considered as compatible with a virus effect:

1. A chicken injected with virus of the MH2 endothelioma five months later developed primary carcinoma of the liver which in another chicken induced leukosis and retrorenal myeloma. From the latter a strain of leukosis was originated which, if inoculated after storage in glycerol, induced typical sarcomas. In two cases epitheliomas developed next to the sarcomatous mass and it was believed that both types of tumors were caused by the same virus.[55]
2. The only transplanted carcinoma so far known originally came from an old hen injected two and a half years before with the virus of MH2 endothelioma. The tumor was carried for many passages but on the second a sarcoma developed, months after injection, at the site where the carcinoma had been injected. This sarcoma was transplanted and subsequently transmitted by filtrates.[56]
3. In work by us[43] on a series of embryonal nephromas of the kidney metastases from either the epithelial or the fibroblastic (fibroma-like) parts of the tumor were observed in some cases while in others typical sarcomatous nodules were present. In one case these nodules proved to be easily transplantable by both cells and filtrates whereas the kidney tumor proved not to be transplantable at all. The gradation established by these observations together with the well known fact that embryonal nephromas in all species metastasize both as carcinomas and as sarcomas strongly suggests that a change toward malignancy has occurred in the metastasizing process and involved a virus effect.

Two other groups of tumors should be reviewed, namely, the naturally occurring fibromas and the sarcomas induced by methylcholanthrene.

Fibromas are often found in chickens. In a series of seven studied by us only one could be

carried through two passages. Often these tumors have features of the slow growing and poorly filterable fibrosarcomas,[43] yet we know that at least in one case a tumor of the latter sort changed into a malignant, easily filterable sarcoma.[43] As for the sarcomas developing after the injection of chemicals, they are so well known[3,57,58] that little need be said about them. The presence of viruses in tumors thus provoked was first affirmed by Carrel, who thought them to be endogenous agents, but was denied by others. The affirmation was again made by McIntosh and Selbie who considered the agents as true viruses, but again these conclusions were denied by others. Isolated cases of filterability of chemically provoked tumors have been reported by at least four authors, as cited by Andrewes[3] and by Maisin.[57,*] On the other hand, other workers believe to have indirectly but conclusively shown the presence of viruses in these tumors by the fact that chickens or pheasants bearing them develop antibodies against known tumor viruses.[59–61]

It has been said that the tumors developing after injection of chemicals cannot be distinguished from those naturally occurring. The statement is true if applied to the original tumor since both types of growths may look alike in the gross and both may show metastases. However, judging by our experience, matters are different when one studies the behavior of both types of tumors on transplantation; for then we can list the following features of the chemically provoked tumors as differentiating them from the spontaneous ones.

1. They lack the marked viscosity due to hyperproduction of mucopolysaccharides, mostly hyaluronic acid.
2. They practically never induce metastases and never hemorrhagic lesions.
3. They probably grow less well in mature hosts.
4. They cannot be adapted to foreign species such as ducks although some of them did grow in ducklings in a number of passages[9] and also in pheasants.[61]

In other words, the sarcomas resulting after injection or chemicals are tumors of relatively low malignancy, their position being probably between that of the naturally occurring fibromas and that of the slow-growing, irregularly filtering fibrosarcomas of the chicken tumor C type.[41]

All in all, it seems extremely probable, even if reproducible results directly proving the point are lacking, that viruses are the proximal cause of the tumors resulting after injection of chemicals. The indirect evidence based on antigenic analogies between the viruses of the "chemical" and the naturally occurring tumors would be entirely satisfactory were it not for the disturbing fact of the frequent presence in chickens, although not in pheasants,[61] of "natural" antibodies against tumor viruses. However, this fact instead of disturbing may be most illuminating if one considers the possible mechanism for the transmission of cancer from the point of view of the virologist.

How are the naturally occurring chicken tumors transmitted in nature? Naturally this is a question that by definition only the virologist asks since the mutationist believes that the viruses are detached components of the cell endowed with the property of incorporating themselves into other cells, not of *infecting* them. Some apparent support for this view could come from the undeniable fact that normal adult chickens living in close contact with others bearing sarcomas, or actually fed the tumor as Rous showed, never contract the disease; the same is true of newborn chicks under the same circumstances as we have repeatedly determined.[9] For the virologist who by definition believes that there must be some sort of epidemiology of tumor viruses, these facts are perplexing and his perplexity may increase if he thinks of the innumerable strains of viruses required to explain as many different tumors, a dogma (that of the immutability of tumor viruses) which although currently honored is undergoing

* We have ourselves a slow growing fibrosarcoma, very similar to chicken tumor C,[41] which proved to be filterable in several tests. The tumor, as far as we know, developed after inoculation of methylcholanthrene underneath the costal edge in the hepatic region. Also, in another publication[1] we mentioned cases suggesting that methylcholanthrene-provoked tumors could have been induced by viruses.

reformation as we shall see later. The epidemiology of many well known infectious diseases is also far from being fully understood, however, and the naturally occurring disease may be in some respects entirely different from the experimental one. Moreover, consolation of a more tangible sort can be found in the following facts:

1. The vast majority of adult chickens living under ordinary conditions have in their blood specific antibodies which neutralize several viruses inducing sarcomas. These antibodies are absent at hatching and develop gradually with aging.[62,*]

2. In experiments by Freire and ourselves[65] it was found that the titer of antibodies for the Rous virus increased many times during a period of five months in chickens living in our animal room together with chickens and ducks of widely varying age bearing sarcomas, lymphocytomas and other virus tumors.

The orthodox student of infection would doubtless conclude without much hesitation that there must be some means of transmission of the tumor viruses to account for these antibodies. Assuming this, to give a reasonable explanation of the appearance of tumors, taking into account the ponderable and imponderable factors that change an infection from latent to manifest, only a step is required. Certainly no more is known of the factors that determine the "spontaneous" infection of the nervous system by the Theiler virus normally present in the intestine, an event which although naturally occurring the experimenters have not been able to duplicate. If, to an increase of antibodies by exposure to a form of neoplasia, we add that the neoplasia most common in chickens, namely, lymphomatosis, manifests itself in typical endemic and epidemic fashion and can be largely prevented by isolation, the story of cancer in chickens starts to have a beginning, a middle and an end. To piece the story together we will review the work on lymphomatosis carried out for the last ten years in East Lansing, Michigan:

1. By strict isolation during hatching and rearing, families of chickens have been raised either entirely free of lymphomatosis for several generations or with an incidence far lower than that present in the ordinary infected flock.[66]

2. The occasional failure to free these isolated birds from the disease may be due to passage of the virus to the progeny before hatching. This may be surmised from the fact that the virus has actually been found in apparently normal embryos and chicks by inoculation into susceptible birds reared in isolation. Also, tracheal and nasal washings from paralyzed birds (*neural* lymphomatosis) when instilled into the nasal passages and trachea of susceptible chicks induced a high incidence of *visceral* lymphomatosis.[67,68]

3. If the isolated birds are mixed with the infected flock they may contract the disease provided the exposure takes place at a very young age.[69]

4. Confirming previous studies[50,70] and using the same susceptible birds, several lines of lymphocytomas have been obtained from naturally occurring cases. Passage of these strains by intramuscular injection of cells results in the rapid induction of a tumor, soon followed by diffuse generalization, as observed in many cases of the naturally occurring disease. If passed by filtrates no local lesions developed, but months later generalized lymphomatosis took place combined in some strains with a bone condition called osteopetrosis.[70–72]

5. As indicative of the large number of virus variants occurring, immunization with one of the passage strains may or may not protect against other passage strains and does not protect against the naturally occurring disease.[73,74]

It would appear futile to claim as some have that lymphomatosis, either diffuse or tumoral, visceral or neural, is not a true malignant disease. All one has to do to convince oneself of the contrary is to watch the general picture of the disease following cell inoculation which is exactly the same as that following inoculation of any other malignant tumor.

* The same study on duck sera and duck variants of the Rous virus[63,64] led to the curious finding that antibodies for the virus, absent in the embryo, were frequently found in newly hatched birds and constantly and in greater strength in older birds. The results were then interpreted as favoring the theory of serologic maturation which, in view of knowledge acquired later, could perhaps be reconciled with that of subclinical infection.

That the disease is epidemic and can be prevented by isolation, that it can manifest itself in infiltrating neural and ocular forms and that it is not much limited by age are characteristics most unusual for cancer, as understood by most. However, are we on that account to commit a grave sin of omission and deny that lymphomatosis is cancer? Is it not more scientific to try to take advantage of the facts disclosed in studying this disease to broaden our knowledge of malignancy? This is what we are going to do, with the hope that in the same way that in the past workers had to reconcile the ideas of *infection* and cancer, workers of the future will have to reconcile the ideas of *contagion* and *cancer*. (See the pertinent comments by Waters[66] on this point.)

The first question to be asked is the following: Do the disclosed facts concerning lymphomatosis serve to explain the propagation of only this particular disease, or could we resort to them in trying to explain the propagation of avian tumors unanimously accepted as cancer? Before attempting to answer this question it would be helpful to take into account the considerations now to be discussed.

What is the nature of the viruses causing tumors and leukoses of birds in relation to ordinary viruses? There is hardly any need to point out fundamental characteristics common to both types of viruses such as the indispensability of living cells for multiplication, similarities in biochemical composition and in size and shape. Other properties, establishing further analogies between ordinary and cancer viruses, such as effects on cells, capacity of variation, masking and immune reactions together with other features pertaining to the tumor itself, will be analyzed in relation to a crucial factor in cancer, namely, the age of the host. We shall refer to it as the "aging factor" which from embryonal life to old age plays an important role in the following phenomena:

Necrotizing Effects on Cells. When the Rous virus is injected into the vein of the amniotic cavity of embryos, no tumors develop but minute hemorrhagic lesions appear in many tissues;[75] the same is true when fragments of tumor and, to a lesser extent, tumor filtrates are inoculated in the chorio-allantoic membrane although in the membrane itself large growths may develop. The "hemorrhagic disease" is far more conspicuous when the veins of newborn chicks are injected.[76] The same results are obtained with a variety of malignant chicken tumors[41] or their variants[9,77,78] when inoculated into embryos or young birds. Microscopically, one generally observes discrete destructive lesions of the capillary wall leading to hemorrhage, with no sign of cancer cells either in the capillary wall or surrounding tissue. However, in the case of two duck variants of the Rous sarcoma that became pseudoneurotropic in the duckling the morphology of these lesions in the central nervous system is characterized by either degeneration of the capillary wall or hyperplasia of its intimal or adventitial layers, frequently accompanied with hemorrhage. The character of these lesions is such that they could easily be confused with others caused by several ordinary neurotropic viruses.[9] Nevertheless in some cases, especially in older ducklings, proliferative phenomena are gradually observed; the vessels are seen occluded by masses of malignant-looking cells of the same sort as those from sarcomas which together with hemorrhagic lesions can be observed in the viscera and other tissues of the duckling, and kill the young host in every case.[9]

Free virus is abundant in all of these non-neoplastic lesions which can be indefinitely maintained as such by passages through immature hosts. The virus, however, never loses its neoplastic properties for whenever an older bird is inoculated with extracts of these hemorrhagic lesions typical tumors develop. The evolution of the virus from destructive to neoplastic can also be observed to occur gradually by inoculation of birds of varying age. Thus from purely hemorrhagic lesions in the chick we see hemorrhagic lesions combined with neoplastic ones in the pullet and, as older animals are inoculated, the preponderance of neoplasia increases until in old animals hemorrhagic lesions are extremely rare

Jackson in South Africa[54] recently found that "in the fowl all gradations occur between lesions of chronic disseminated focal encephalitis and gliomas, often in the same brain." He states later that "I believe that glioma of the fowl will

prove to be nothing but a proliferative response to a specific infectious agent."

Blakemore and others[79,80] in England found that strains of lymphomatosis virus infecting chicks produced a purely necrotizing mild disease (which highly increased in severity after passages) involving the heart and liver of the bird, whereas the more resistant birds developed typical lymphomas. Blakemore considers the latter lesions to be the chronic state of an acute disease.*

Thus the viruses of avian cancer studied in this respect, like the fibroma virus and other infectious agents previously reviewed, can manifest themselves either as destructive or as neoplastic. No doubt other factors are operative in this respect, e.g., an inherent property of the tissue that will make it react to the virus by neoplasia, as for instance the chorio-allontoic membrane, the relative virulence of the virus[75] and also the animal species.[11] But most important for our problem is the age factor.

Tumor Growth, Metastases Formation and Transmissibility by Cells. On analyzing the influence of age upon these features of the tumor we must consider both the age of the host and the age of the tumor.† As to the age of the host, it is responsible for basic differences such as the following: In the young a minimal amount of virus will induce rapidly growing tumors, often generating metastases and hemorrhagic lesions,[62,76] and transmissibility either by cells or by filtrates is usually successful.[82–84] In the adult host the reverse is true: Larger amounts of virus are required to induce tumors, their growth is slow,[62,76] hemorrhagic lesions are a rarity, metastasis formation diminishes and, as to transmissibility, it is not always feasible either by cells or by filtrates. As to the age of the tumor, its influence becomes evident in the adult host in the following manner: Transmissibility of the tumor by cells, which is somewhat inhibited in the adult host, becomes much more difficult if the tumor is old. If such old tumors are transmissible by filtrates, that is by the virus, the incidence of metastases is significantly less in the second generation of hosts than if the filtrate came from a young tumor.[82,83] Although not statistically significant, there was a trend indicating that this initial reduction in metastases remains constant in the course of further passages. Other observations in the same study are concerned with the independence of induction of metastases from induction of hemorrhagic lesions, the former being the product of cells and the latter the product of free virus. Each of these lesions occurs preponderantly in different organs: Hemorrhagic lesions are directly affected by the amount of virus injected; metastases are not.[76,82]

We have in the observations just noted convincing proof that besides quantity the *quality* of the virus alters basic features of malignancy. Since the altered features in tumors induced by *virus alone* persist from host to host, as for example the diminution of metastases, it is clear that under the influence of the aging factor the virus has changed. This change is of the greatest importance to discussion of the following subject:

Variation of Viruses. That the virus in this *changed* state, and *only in this state*, is capable of variation is shown by the fact that at the age of the host when this change occurs, from five to ten months, the Rous sarcoma virus can easily be adapted to other species of birds.[85] A tumor from a chick if inoculated by cells into a duck may induce a tumor which can also be maintained but for a short number of passages. A tumor from an old chicken generally fails to take in a duck but if it does adaptation to the duck follows. Besides the age of the donor the age of the recipient also conditions the variation of the virus. Thus turkeys can be infected with virus within the first ten weeks after hatching; guinea fowls, within the first five weeks and ducks only within the first day. Pheasants are more or less susceptible for at least many months.[77,78] On the other hand, pigeons are entirely unsusceptible to chicken viruses; but after this virus has varied

* Further studies by Asplin[81] on the subject may cast some doubt on the validity of Blakemore's conclusions; for evidence has been found that can be interpreted as indicating that the non-neoplastic, contagious disease of the young, the so-called chick disease, and lymphomatosis are independent diseases although they can frequently occur in the same individual. The situation is extremely interesting and calls for further work. Possibilities that masking and variation of the virus play a part in the phenomena observed must obviously be considered.

† Many of the observations we quote in this section, as well as in others preceding or following it, belong to a series of unpublished articles by Dr. P. M. Freire and ourselves.

in ducks, they can be infected at any age although the tumor can be maintained for only a limited number of passages.[86,87,*]

Every one of these variations of the virus occurring with inoculation into another species results, among other changes, in new types of tumors, and the proof that the variation has been absolute is that a duck variant, for example, if inoculated back into a chicken will induce the same type of tumor it induced in the duck. Sometimes this duck variant, or others, may induce new lesions in the chicken such as osteopetrosis, a naturally occurring condition in chickens,[70] with or without lymphomatosis. This indicates further virus variation.[77] Reversion to the original Rous sarcoma may have been observed in one case.[88]

Thus through variation of a single virus many different tumors and other conditions as well can be induced. Therefore, we cannot accept the criticism[2] that "the changes obtained in tumor type are too slight to lessen in any considerable degree the magnitude of the theoretical problem presented." True, we did not by variation of the Rous virus obtain all the transmissible mesodermal malignancies normally occurring in chickens (such as osteochondrosarcomas and endotheliomas) but we have obtained a histiocytoma,† a lymphocytoma and many sarcoma variants selectively affecting bones, skin and central nervous system.[77,78,88] One can easily conceive that had we set up experiments using the same or other tumor viruses but exclusively devised to obtain variants, many more tumor types could have been produced. One must remember what has already been pointed out concerning epithelial tumors, especially embryonal nephromas. Also, as specially pertinent to the problem, one must remember here the occurrence of virus complexes which, according to the circumstances, induce different types of leukoses and also endotheliomas and osteochondrosarcomas, a state of affairs so suggestive of virus variation.[50,55,56,89]

Indeed, the facts just reviewed indicate a great power of variation of avian tumor viruses and make it unnecessary to postulate that a different virus is needed to explain each type of tumor.* Conceivably, the virus which in the chicken induced the original Rous sarcoma could, through variation, have induced in the same host the same variety of tumors experimentally obtained in other species. Thus the viruses of the latter tumors, injected into the chicken, reproduce in these hosts the tumors they usually induce in the other species.

Masking of the Virus and Regression of the Tumor. As stated previously, a change occurs in the virus in the adult animal. This change proceeds to its final form in the old host. Transmissibility of the tumor by cells becomes difficult as the host ages and by filtrates is often impossible. The virus is masked.

It was known for a long time and the observation is often quoted that the Rous tumor may go through long phases of unfilterability in which case it can be maintained only by cell passage.[90] It was also known that the older the tumor the less filterable it is.[91]

In our work with Freire[83] we have shown that masking of the sarcoma virus, besides being conditioned by the age of the host and the age of the tumor, is also conditioned by the source material, cells or filtrates, employed in inducing the tumor. Concerning the first factor we found that masking occurred in twenty-seven of forty-

* The situation created in this case is the following: The duck tumor virus is capable of infecting the pigeon but not of adapting itself to this species. The tumors induced are the result of a heterologous infection,[77] that is, the infection induced by a virus which in the original homologous species induces indefinitely transplantable tumors or other lesions. Studies with P. R. F. Borges[87] indicate that the virus in the pigeon tumor becomes masked even in young tumors growing in young hosts, and can be unmasked by transplanting tumor cells into homologous hosts such as ducklings. Therefore, the tumor virus seems to undergo in the heterologous species the same process of masking that in the homologous species is brought about by age, as will be seen in the following section. Analogies between the pigeon tumors and papillomas in domestic rabbits[40] seem clear.

† This is a tumor designated as strain E[77] which consisted of a combination of large, clear, sarcoma-like cells and smaller, rounded lymphoblastic cells.

* We wish to point out in passing that tumor viruses are far better agents to study virus variation than ordinary viruses since obviously many more differences can be detected between newly built tissues than between destroyed tissues. These differences may be observed in the general architecture of the tissue, its ground-substance and its cells; also in its rate of growth in homologous and heterologous species, metastasis formation and other features.

four Rous sarcomas grown in chickens about fifteen months old whereas it occurred in only six of thirty-eight tumors grown in chicks inoculated at the age of two weeks. The aging factor, which apparently exerted its effects in an all-or-none way, acted preferentially on the tumors induced by filtrates as if the virus, thus unprotected, was more vulnerable to it; but it also acted on the virus in older tumors protected by the cell. When the virus became masked, the diminution in transmissibility by cells and the formation of metastases, already evident before masking, became definitely more pronounced in the old host. It seems obvious that the change in the virus proceeded to destruction of the virus, although so far it had not progressed beyond what seems a transitory state of degradation or impairment of some sort. For as long as the cells are active, inoculation into a chick will produce the hemorrhagic disease or tumors from which free virus can be secured in full vigor and activity.[83] A step further, however, and the change is fully accomplished, to the annihilation of the virus as was to be expected. The tumor becomes totally intransmissible, regression takes place and solid immunity is established. This occurred in our experiments[84] in at least 15 per cent of 192 adult or old chickens. Of 1,500 chicks bearing the same tumor not a single case of regression occurred. Other workers have made similar observations.[92]

We emphasize the role played by age in the previously described phenomena since, for one thing, we do not know conclusively precisely what factors are responsible for them. We studied the possible role of antibodies in the masking process and found no difference in the content of viral antibody following the growth of filterable or non-filterable tumors. The only suggestive finding was that some chickens in which antibody was absent before and after tumor growth developed solely filterable tumors, and chickens that developed non-filterable tumors seemed to have more antibody before inoculation than those that developed filterable tumors.[65] More about this point will be said later.

Analogies between masking of the sarcoma virus and masking as described in ordinary viruses are obvious. It may be that the phenomenon in chicken tumors is the result not of one but of several of the causes that lead to masking of ordinary viruses, but speculating on this point would take us too far from our concrete objective. However, a comparative description of the masking of papilloma virus is particularly relevant.

The papilloma virus frequently present in a free state in its natural host, the wild rabbit, becomes masked at once in the growths it induces in the domestic rabbit;[40] yet the wild rabbit develops viral antibodies just as well as the domestic rabbit, and the antibodies also develop in domestic rabbits grafted with carcinomas, derived from the papilloma, for a long number of passages. However, by grafting young hosts with this tumor, papilloma virus was recovered in three successive passages.[93] There are indications that masking, when it occurs in the domestic rabbit, is due to other causes than in the wild rabbit in which the phenomenon seems to be due to specific antibody.[94,*]

In summary, from embryonal life to old age the aging factor suppresses, first of all, the destructive effects of the virus, changing it into a tumor virus. Thus the production of neoplasia is the first manifestation of resistance. Later, the aging factor lowers the susceptibility of the host to minimal infective doses, inhibits the growth of the tumor, depresses its capacity to be transplantable by cells and to produce metastases, and causes the virus to vary. Finally, it induces masking of the virus and tumor regression. At this point we have obviously lost the tumor. But before reaching this point it would appear that we first lose the virus when tumor filtrates become negative; however this is not the case. As long as there is a growing tumor there is a virus because although in a degraded and masked form we can expose it easily enough by passing the tumor by cells into young hosts. Again the "cancer" virus behaves as a destructive virus which if inoculated into older hosts

* Detailed information on these, as on so many other points of this important investigation by the workers of the Rockefeller Institute, is to be found in the papers published by Rous, Kidd and others in the Journal of Experimental Medicine since 1934. Many data are given by Rous in his article[2] and other reviews.

will begin again the process described. Figure 1 represents these events graphically.

From events in this cycle a concept of great interest seems to emerge, namely, that a "cancer" virus can exist both in a *degraded, masked* form and in a *vigorous, free* form. Some speculation on this situation seems appropriate.

The degraded masked virus in chicken tumors cannot stand separation from the cell either because it is very vulnerable to surrounding influences during processing of the tumor or for other reasons. Could it then be that more gentle methods such as those recently used by some workers[95,96] permit the extraction of degraded but still active viruses from several mammalian growths? Could the same be true for some, at least, of so many other reported results which cannot be reproduced at will precisely because of the fragility of the virus? Could one consider the chemically provoked tumors in birds to be produced by degraded viruses? The same question can be asked concerning first, the virus of the rabbit papilloma which seems to undergo a progressive series of changes in the transplantable cancers derived from the papilloma until, after many transplants, it is no longer recognizable as an antigen;[93] and second, concerning comparable antigens which may induce efficient protective antibodies, such as are found in tumors like the Brown-Pearce rabbit carcinoma.[97] Closely linked with these questions is the following: How many of these hypothetical viruses would be capable of reverting to a free, vigorous form as in the case of avian sarcoma viruses? Or, would this reversion be biologically impossible with viruses too far gone in their degradation? These may be very important points to remember when pondering the cause of tumors of unknown etiology.

Concerning virus variation and tumor regression one has to point out that at the same period, in the aging host, when the virus shows signs of degradation and before becoming masked, it can vary. Thus both phenomena, *variation* and *degradation*, may be related. According to the orthodox view, variation is the transformation of one virus type into another, both remaining free and always active. However, enlarging the concept, one could well consider degradation and masking as a form of variation.

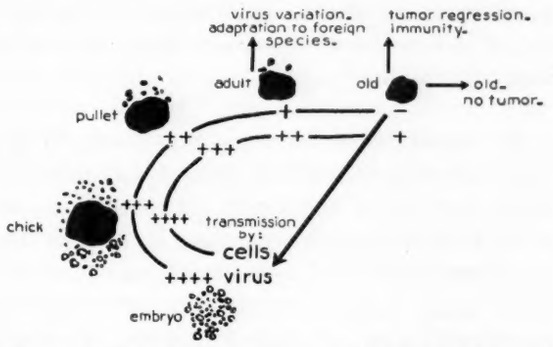

FIG. 1. Cycle of the Rous sarcoma virus as conditioned by the age of the host, the chicken. In the embryo only non-neoplastic hemorrhagic lesions (circles) occur; in the chick both neoplastic and hemorrhagic lesions appear, with an abundance of metastases (dots); in the pullet neoplastic lesions predominate, with a slight diminution in metastasis formation; in the adult hemorrhagic lesions are few and rare, tumors grow slowly and the diminution in metastasis formation becomes evident (impairment of malignancy with concomitant variation of the virus); in the old host hemorrhagic lesions are absent, tumors grow badly and regression occurs frequently followed by solid immunity. Transmissibility parallels this sequence by diminishing as malignancy declines. Transmissibility by filtrates is first and more radically affected. The virus, however, can be recovered by inoculation of tumor cells from the old host before signs of regression into embryos and chicks as well, and the cycle begins all over again. The cycle is subject to variations corresponding to the relativity pertaining to age.

Kidd and Rous[98] adopted this view in connection with the transformation of papillomas into cancers. Could then one suppose that the masked virus in the chicken tumor undergoes still further lethal changes leading to its complete destruction or inactivation? The cancer cell, deprived then of its impelling force would no longer be viable and regression would occur.

We do not know the exact nature of the aging factor and whether it consists of one agent responsible for all the effects on tumors or whether several agents are involved.

In a general way the development of antibodies against the sarcoma virus parallels the

development of the aging factor. For this antibody is absent at hatching, increases with age,[62] also after tumor growth,[65] and is capable of protecting chicks for many months against the virus.[9,99] However, no quantitative relation was found between the antibody content and metastases formation, regression of tumors and subsequent immunity.[65] The same situation has been found in the case of regression of papillomas in domestic rabbits.[100]

It would seem natural, therefore, to invoke other forces, which may act in concert with the virus antibody, to explain the effects on the tumor including its regression. However, if degradation and masking of the virus and tumor regression are further manifestations or consequences of virus variation perhaps no quantitative relation would be needed, in view of the largely unpredictable vagaries of virus variation, between the cause, which could be the antibody, and the occurrence of variations.

* * *

The reversion of the virus to its free, vigorous form in the immature host and the fact that immaturity is often a condition *sine qua non* for infection suggest that the young host is the critical link in maintaining and spreading the disease. At this point we take up again the discussion started before on the epidemiology of avian cancer.

The virologist could imagine that "cancer" viruses infect young hosts in which they induce very mild, subclinical, non-neoplastic conditions* close to the carrier state. Later in life these latent viruses through the provocative effects of carcinogens would vary and induce different tumors. When the virus thus becomes a cancer virus, its contagious power is lost. Nevertheless, although the point has probably never been thoroughly investigated,* the only viruses with a clear epidemiologic value found latent in young hosts[67,68] and to which these hosts are either specially or exclusively receptive[69] are those of lymphomatosis. However, since these viruses can manifest themselves clinically either shortly after exposure, that is in the young host, or much later in life, indicating a long period of latency, the virologist could venture the following hypothesis: In a number of these individuals infected early in life with the virus of lymphomatosis the virus, after having induced or failed to induce a non-neoplastic disease,[80,81] remains latent; later in life it varies and instead of lymphomatosis it induces sarcomas and other types of malignancy. In favor of this supposition there is, first, the existence of those virus complexes producing both tumors and lymphoid malignancy, presumably through virus variation, and second, the proved power of variation of sarcoma viruses which may lead to lymphoid tumors and osteopetrosis. For the virologist, then, the neutralizing antibodies for the Rous and other tumor viruses, present in most adult chickens, could be the result of subclinical infection with sarcoma viruses; but more likely, although not entirely excluding the latter possibility, they could be the result of the immunologic response to viruses of contagious lymphomatosis or variants thereof which would have antigens in common with the viruses of sarcoma and other tumors. This hypothesis could perhaps be demonstrated if it were found that sera from chickens belonging to flocks entirely or largely free of lymphomatosis did not have antibodies against tumor viruses or had them in low levels. Also, if one could show that the lymphomatosis virus inoculated into certain hosts prepared by carcinogens was capable of inducing sarcomas or other

* If non-neoplastic diseases, hemorrhagic or otherwise, induced by "cancer" viruses occur under natural conditions, they should be in no way comparable to what is observed experimentally after injection of immature hosts with these viruses which have been brought, through passages, to an unnaturally high degree of virulence. The situation would be the same as if naturally occurring tumors, relatively slow growing, were compared to the disease developing after inoculation of the passage tumors.

* We have frequently inoculated chicks with extracts of tissues from other chicks previously injected with methylcholanthrene, with the hope of detecting viruses there present. Results were always negative. One may add that the chemical induces pronounced necrotizing and inflammatory lesions in these young hosts.

tumors. Both studies are now being carried out in our laboratory, so far with encouraging results.

* * *

The facts reviewed leave no doubt in the virologist's mind that the viruses of mesodermic avian malignancy do not differ fundamentally from other viruses. This conclusion would naturally lead to another, namely, that malignancy is only a phase in the activity of these viruses. The virologist is aware that his conclusions, even in reference to avian cancer, are not accepted by most workers. Despite this, and at the risk of seeming stubborn, he may go so far as to extend further the logic of his conclusions by suggesting that if some "cancer" viruses behave very much like some ordinary viruses, some ordinary viruses may behave like some cancer viruses; that is, these ordinary viruses would invade the young host, remain latent and, under the influence of a carcinogen, vary so that they impel the cell to proliferation, not to necrosis, and finally degrade, become masked and thus are not easily to be recovered. To put such a suggestion to the experimental test the virologist would then inoculate any such ordinary virus into hosts prepared with carcinogens and hormones in such a way that, theoretically, they would react as do hosts in the cancer age.

But which virus, which species and which carcinogen or hormone should one select? Although it is a plain case of groping in the dark, it would seem logical to begin with viruses which although ultimately destructive are endowed with a certain power to stimulate cell growth such as those of the papilloma and fibroma of rabbits which so easily induce cancer or a condition close to it if acting in concert with carcinogens.[3,10] It would seem logical, also, to choose viruses with a broad host range although occurring in distinctive types or variants in the respective species. Viruses of the pox group fulfill these requirements.

We have been actively engaged in work along these lines during the last three or four years; even so we believe that the subject has just been scratched on the surface. It is not our intention here even to summarize whatever has been accomplished in the course of many long and often unrewarding experiments, yet it may prove useful to mention a few observations. Preparation of the skin of chicks with methylcholanthrene makes possible a vaccinial infection that in normal chicks of the same age is either not produced or is not evident. The same procedure in rabbits changes profoundly the lesions ordinarily produced in these animals by vaccinia. Virus variation was observed in the latter case. Painting of the skin of chicks with methylcholanthrene caused development in the treated area of fowl pox which is produced by a virus known to be latent in many flocks. This event was never observed in untreated control chicks. On continuation of the methylcholanthrene treatment a variety of largely proliferative, chronic lesions developed from which pox virus could be isolated for many months in succession. Injections of testosterone caused a pronounced flaring up of these lesions. Among them typical squamous cell carcinomas were observed.

These results and many others that we could quote from other experiments are, no doubt, scattered and incomplete; yet, in the mind of the virologist they fully justify further efforts aiming to prove conclusively the hypothesis that cancer may be the result of ordinary viral infection.

SUMMARY

In order to explain satisfactorily the basic features of cancer a theoretical *cause* of cancer should be endowed with the following fundamental properties: (1) It should exhibit an affinity for cells and induce them to grow while multiplying along with them. (2) It should be specific for cells so that the same lesion is repeated, yet able to change so that many different lesions are produced. (3) It should be able to remain in a latent state in tissues and be conditioned by genetic and surrounding conditions such as those attending old age. (4) It should be capable

of existing either in a free or in an occult state. Viruses fulfill all these requirements. Nevertheless the so-called virus or infectious theory of cancer is not at all popular, most workers favoring endogenous theories. Arguments for and against these doctrines are reviewed, especially those centering on comparisons between bacterial virulence and cell malignancy and the nature of the principles changing bacterial types.

The most important argument supporting the virus theory is the undeniable fact that a number of cancers are induced by viruses, of which the most interesting in some respects are those of avian cancer. By studying the phenomena attending the infection of chickens from embryonal life to old age the conclusion is reached that these viruses do not differ fundamentally from ordinary viruses, for in the immature host they induce necrosis instead of neoplasia, and in the cancers they cause in older hosts the virus undergoes a process of degradation manifested first by a depression of the malignancy of the tumor (as indicated by transplantability by cells and metastasis formation) and later by unfilterability of the tumor, that is, masking of the virus. Simultaneously with these events the virus may vary in many forms which cause as many different tumors, as shown when foreign species are infected. These phenomena are discussed in relation, first, to the possible existence in cancers of "unknown etiology" of causative degraded viruses which cannot be demonstrated by ordinary means, and second, to tumor regression.

The degraded, masked virus reverts to a vigorous, free form by grafting the tumor into young hosts. This fact together with newer knowledge on contagious lymphomatosis is discussed in relation to the mode of spread of chicken tumors.

What has been learned about avian cancer and other types of virus cancer leads to an important question, namely, whether ordinary viruses are capable of inducing cancer under certain conditions. This possibility is discussed and an experimental plan of attack is outlined.

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Clinico-pathologic Conference

Severe Anemia with Hepatosplenomegaly and Cardiac Failure*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, L. P. (No. 168952), was a white married merchant seventy-five years of age, who entered the Barnes Hospital for the first of five admissions on February 22, 1949, complaining of weakness, shortness of breath and swelling of the legs. Family and past histories were irrelevant. The patient was apparently well until three years before admission when he developed numbness and tingling of the left leg unassociated with any motor disturbance. About the same time he noted weakness which progressed thereafter until admission. For many years he had been aware that the left side of his abdomen was much more prominent than the right side and three months prior to entry he felt a mass in that area. At that time shortness of breath on exertion appeared and subsequently increased. Six weeks before entry the patient's abdomen began to distend and two weeks later progressive swelling of the legs appeared. His complexion became sallow and two weeks before entry he noted numbness about the rectum and fecal incontinence. He was forced to remain in bed although prior to this time he had continued to work regularly.

At the time of admission physical examination revealed the temperature to be 37°C., pulse 72, respirations 24 and blood pressure 140/80. The patient was an elderly man who appeared chronically ill. Pallor and dependent edema were marked. The skin showed senile changes but there was no purpura. Several soft, spongy lymph nodes were felt in the axillas, one measuring 1½ cm. in diameter. The pupils reacted normally to light and accommodation. Examination of the fundi revealed sclerotic changes in the arterioles and hemorrhages but no exudate was seen. Examination of the upper respiratory tract was within normal limits except for pallor of the mucous membranes. The neck veins were somewhat distended. Examination of the lungs revealed dullness to percussion at both bases, particularly on the left. Scattered rales were heard throughout both lung fields. The heart was moderately enlarged to the left. The sounds were of good quality and the rhythm was regular except for occasional premature contractions. A harsh, low-pitched, grade III systolic murmur was heard over the entire precordium but was more prominent at the apex. The abdomen was distended and signs of ascites were evident. In the left upper quadrant a large mass, presumably spleen, was palpated. It extended below the level of the umbilicus. The prostate was enlarged, symmetrical and soft but no other masses were felt on rectal examination. Dependent edema extended up to the costal margin. His spine was rather stiff and motion was limited. Aside from absent knee and ankle jerks there were no abnormal neurologic findings.

The laboratory findings were as follows: Blood count: red cells, 2,690,000; hemoglobin, 7.2 gm.; white cells, 6,500; differ-

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ential count: basophiles, 8 per cent; myeloblasts, 6 per cent; myelocytes, 9 per cent; metamyelocytes, 3 per cent; band forms, 12 per cent; segmented forms, 27 per cent; lymphocytes, 16 per cent; monocytes, 19 per cent. The segmented forms were deficient in granules; anisocytosis and poikilocytosis were marked; platelets, 560,000; reticulocytes, 9.4 per cent. Urinalysis: specific gravity, 1.021; albumin, trace; sugar, negative; sediment, rare red blood cell. Stool examination: guaiac negative. Blood Kahn test: negative. Blood chemistry: non-protein nitrogen, 33 mg. per cent; total protein, 5.7 gm. per cent; albumin, 4.1 gm. per cent; globulin, 1.6 gm. per cent; chlorides, 99 mEq./L.; cephalin-cholesterol flocculation test, ±; thymol turbidity test, 21.5 units. Electrocardiogram: within normal limits. Roentgenogram of the chest: "The heart appeared moderately enlarged to the left. The hilar shadows were increased. A uniform, slightly nodular density was seen in both lung fields, and one rounded opacity in the right cardiophrenic angle, which may have been due to pulmonary vascular engorgement, was noted. Changes consistent with broncho-pneumonia in the left lower lobe were also present. All the bones visualized had abnormal opacity suggestive of extensive metastatic carcinoma."

Shortly after entry an abdominal paracentesis was performed but only 100 cc. of straw-colored fluid were obtained. The fluid had a specific gravity of 1.013, a protein content of 2.3 gm. per cent and a total cell count of 2,750. A sternal puncture was attempted but no clumps of marrow could be obtained. Sternal biopsy was done by trephine, and a small piece of bone was aspirated; microscopically, it revealed diffuse fibrosis but no functioning marrow. The patient received three whole blood transfusions; and although he was not symptomatically improved, he left the hospital to attend to urgent business with instructions to return within one week. Before being discharged on March 1, 1949, he was digitalized and a low salt diet was prescribed.

For the next ten days his symptoms remained unchanged; when he was readmitted on March 10, 1949, the physical findings were as before. The significant changes in the laboratory findings were that the red cell count had risen to 4,140,000 and the hemoglobin to 12.1 gm. Blood non-protein nitrogen was now 71 mg. per cent. The electrocardiogram had changed appreciably in that the T waves were diphasic in Lead I and inverted in Leads II and III, and the S-T segments were slightly depressed in Leads I and II. He received two more transfusions of whole blood and was maintained on digitoxin. At the time of discharge on March 16, 1949, his non-protein nitrogen was 63 mg. per cent.

After he returned to his home the patient was attended by a chiropractor and during this period lost 12 pounds in weight. He refused to disclose the nature of the chiropractor's therapy. He had not taken digitalis regularly. Shortness of breath had increased markedly as had his weakness and he returned on April 16, 1949, for more transfusions.

Physical examination now revealed that the hemorrhages in the eye grounds were no longer visible. Moist rales were heard over the lower two-thirds of each lung field. The firm, irregular edge of the liver could be felt 8 cm. below the right costal border. The laboratory data included a red count of 3,440,000, hemoglobin 9.7 gm. and white cells 7,900. The differential count revealed 10 per cent basophiles, 4 per cent myelocytes, 3 per cent metamyelocytes, 8 per cent band forms, 15 per cent segmented forms, 22 per cent lymphocytes and 38 per cent monocytes. Urinalysis showed only a trace of albumin. The non-protein nitrogen was 38 mg. per cent. The patient was given 1,000 cc. of whole blood without any reaction. At the time of discharge on April 18, 1949, his hemoglobin was 10.8 gm. per cent and he felt symptomatically improved.

Soon after leaving the hospital the patient's heart failure became more severe as

evidenced especially by weight gain and dyspnea. Because of dyspnea and weakness he was confined to bed and on May 18, 1949, he returned to the Barnes Hospital for the fourth time. The physical signs were essentially as before although the patient was much more dyspneic than he had been previously. Signs of fluid were noted in the left chest. The abdomen seemed more distended and the spleen was larger. The laboratory data were as follows: Blood count: red cells, 2,940,000; hemoglobin, 9 gm.; white cells, 9,000; differential count: basophiles, 6 per cent; myelocytes, 5 per cent; metamyelocytes, 3 per cent; band forms, 6 per cent; segmented forms, 21 per cent; lymphocytes, 31 per cent; monocytes, 28 per cent; there were 14 blast forms and 2 nucleated red cells per 100 white cells. The urine showed only a trace of albumin. The non-protein nitrogen was 45 mg. per cent. Roentgenogram of the chest revealed moderate cardiac enlargement, fluid in the left pleural cavity and bilateral peribronchial thickening. The appearance of the bones was as before. The electrocardiogram showed little change. During his hospital stay the patient received three blood transfusions and additional digitoxin. His dyspnea decreased. He was discharged on May 23, 1949.

During the interval between his fourth and fifth admission the patient's weakness progressed. He felt comfortable in bed only while lying on his left side. In any other position he noted abdominal pain and dyspnea. He took digitoxin only irregularly. He was incontinent of feces and urine and for forty-eight hours prior to entry he had watery diarrhea. During these last two days swallowing caused great pain and at times the patient was irrational. He was admitted for the last time on August 19, 1949.

Physical examination revealed emaciation. The patient was dyspneic on the slightest exertion and marked edema was present. He complained of pain when he moved to any position other than the left lateral decubitus. His skin was very pale. There was no generalized lymph node enlargement. Many moist rales were heard throughout both lung fields. The heart sounds were unchanged and there was no friction rub. Ascites, hepatomegaly and splenomegaly persisted.

The laboratory findings were as follows: Blood count: red cells, 2,830,000; hemoglobin, 7.2 gm.; white cells, 46,000; differential count: basophiles, 2 per cent; myelocytes, 39 per cent; band forms, 8 per cent; segmented forms, 28 per cent; lymphocytes, 8 per cent; monocytes, 15 per cent; platelets, only a few seen. Blood chemistry: nonprotein nitrogen, 63 mg. per cent; total proteins, 5.5 gm. per cent; albumin, 3.4 gm. per cent; globulin, 2.1 gm. per cent; chlorides, 107 mEq./L.; CO_2 combining power, 34.3 mEq./L.; calcium, 8.0 mg. per cent; phosphorus, 6.5 mg. per cent; alkaline phosphatase, 11 Bodansky units; cephalin-cholesterol flocculation test, 1+; thymol turbidity, 4.1 units; total bilirubin, 1.26 mg. per cent; sodium bilirubinate, 0.99 mg. per cent; bilirubinglobin, 0.27 mg. per cent.

The patient was obviously terminal on arrival and soon after entry stupor and Cheyne-Stokes respiration were noted. He died quietly on August 20, 1949.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case was selected primarily because of its hematologic interest, but in addition to the underlying blood dyscrasia we shall in the course of our discussion attempt to explain both the cardiac failure and the neurologic signs. Dr. Anthony, do you have any comments to make in regard to the x-ray films?

DR. DALLAS D. ANTHONY: As was noted in the protocol, the most striking finding in the films was the density of all the bones visualized. The medullary cavity was scarcely visible. The marked opacity of the bones strongly suggested to us the possibility of osteoblastic metastatic carcinoma. A number of tumors could give rise to such a roentgenologic picture but probably the most common one would be carcinoma of the prostate.

DR. ALEXANDER: The fact that the bone marrow was involved by the disease process was further evidenced by the fact that when bone marrow aspiration was attempted no marrow could be obtained. In addition then to the apparent destruction of bone marrow and the severe anemia the patient also had abnormal white and red cells in his peripheral blood and a large liver and spleen. I shall ask Dr. Carl Moore to discuss the general problem presented here.

DR. CARL V. MOORE: The changes observed in the peripheral blood of this patient were comparable either with chronic myelocytic leukemia or a myelocytic leukemoid reaction. The first step, therefore, in establishing the diagnosis was to differentiate between these two possibilities, and for this purpose examination of the marrow was of maximum help. In chronic myelocytic leukemia the marrow in addition to being very cellular shows hyperplasia and immaturity of the granulocytic elements with a striking decrease in nucleated red blood cells. Sometimes, in myelocytic leukemoid reactions, the marrow may simulate that of true leukemia, but often one may identify abnormalities which have caused the leukemoid reaction, for instance, invasion by tumor cells, presence of granulomatous lesions or myelosclerosis. In this patient examination of the bony fragment obtained at the time of bone marrow biopsy showed quite clearly the changes of myelosclerosis. The otherwise "dry" sternal aspiration is what one would expect with diffuse fibrosis of the marrow cavity. The enlargement of liver, spleen and lymph nodes can be explained on the basis of extensive extramedullary hematopoiesis. While some of the immature white cells which were poured into the peripheral blood could have come from less extensively involved areas of the marrow, most of them presumably were derived from these areas of extramedullary blood formation. Furthermore, since the bones were of such great density on roentgenologic examination, it is probable that the patient had osteosclerosis as well as myelosclerosis.

The roentgenologists, however, interpreted the skeletal changes not as osteosclerosis but as being caused by osteoplastic carcinomatous involvement. It could well be argued that certain carcinomas cause localized areas of marrow fibrosis when they metastasize to bone and that we may have sampled one such area. If that were true, one would have to assume that there were extensive metastases to the liver and lymph nodes and explain the splenomegaly on the basis of congestion with or without metastases. Myelosclerosis and osteosclerosis would seem much more likely.

One more objection to the diagnosis of myelosclerosis may be made. The total known duration of the illness in this patient was only about three and a half years. Myelosclerosis usually runs a much more chronic course. During the first years of the disease, however, patients may feel so well that they are unaware of any abnormality. It is only when anemia develops or the spleen becomes so large as to cause a sense of heaviness in the upper abdomen that they become conscious of the disease. The actual duration of this man's illness, therefore, may well have been considerably greater than the medical history indicates.

Lastly, a word should be said about the nature of myelosclerosis. In my discussion I have followed the lead of numerous workers and assumed that the peripheral blood changes were those of a leukemoid reaction. According to this concept, fibrosis occurs in the marrow for some unknown reason, areas of extramedullary hematopoiesis form as a compensatory phenomenon and immature cells reach the peripheral blood because the extramedullary centers are not as efficient as is normal marrow in regulating the delivery of cells. Many hematologists and pathologists, on the other hand, regard myelosclerosis and osteosclerosis as variants of chronic myelocytic leukemia. They believe that in most instances the marrow changes are secondary rather than primary. Although it seems to me that the bulk of the evidence favors the concept of a leukemoid reaction rather than

true leukemia, it must be recognized that neither view has been proved.

DR. ALEXANDER: Thank you very much, Dr. Moore. In extramedullary hematopoiesis, I presume, the spleen and liver assume the function normally borne by the bone marrow and most of the cells may be made in those two organs.

DR. C. V. MOORE: That is correct. If one believes that the marrow change in these cases is primary and the extramedullary blood formation is compensatory in nature, one can postulate that the fundamental stimulus to blood cell production, whatever it might be, is still operative. In hypoplastic anemia, however, when there is marrow failure because this hypothetic stimulus has been lost, there is also no stimulus for the formation of extramedullary foci and none forms.

DR. ALEXANDER: What makes the liver and spleen so large?

DR. C. V. MOORE: Much of the enlargement results from the hematopoietic tissue. How much increase there is in actual splenic parenchyma or fibrous tissue I do not know.

DR. ALEXANDER: Does the spleen also destroy these cells or is it only the site of their production?

DR. C. V. MOORE: Probably the larger the spleen gets the more cells it destroys either by a process of sequestration and stasis or by actual phagocytosis.

DR. W. BARRY WOOD, JR.: Dr. Alexander, could we ask Dr. Moore to give us a rough idea of the number of cells involved in this disease? How many red cells does the normal marrow of adults produce in a day?

DR. C. V. MOORE: For a man whose red cell count is 5,000,000 per cu. mm., whose blood volume is 5,000 cc. and whose red cells survive in the circulation for an average of 120 days, the bone marrow must make 200 billion cells per day to maintain the count.

DR. ALEXANDER: What explanation do you have for the neurologic complaints this patient exhibited?

DR. C. V. MOORE: They were primarily those of peripheral neuritis. I do not know what caused them. Deficiency disease, pressure on nerves, actual invasion of nerves as occurs in leukemia, etc., are all possibilities.

DR. ALEXANDER: Recently the use of vitamin B_{12} in such cases has been reported to be quite effective. Do you know of any substantiating data on this point?

DR. C. V. MOORE: Only that which Dr. William B. Bean reported recently in these cases. One of the most amazing things about his report was that improvement in the neurologic changes occurred within hours after B_{12}, whereas it takes weeks with thiamine. It is not clear to me, however, how long the B_{12} effect persists.

DR. ALBERT I. MENDELOFF: Is pain common in myelosclerosis?

DR. C. V. MOORE: Deep bone pain is not unusual, and the aching may be severe.

DR. ALEXANDER: Is it true that radiation therapy is sometimes beneficial in such situations?

DR. C. V. MOORE: According to most clinical observations, if a patient with myelosclerosis is given radiation to the spleen in amounts comparable to that which would be given to a patient with leukemia, the results are detrimental. Similarly, splenectomy is reported to shorten the life of patients with myelosclerosis. There are times, however, when the spleen becomes so large and so uncomfortable that cautious x-ray therapy is necessary to give the patient some relief. We have done this several times without apparently doing harm.

DR. ALEXANDER: Is the life of a transfused cell in patients with myelosclerosis the same as in a normal individual?

DR. C. V. MOORE: I don't know if that information is available. We have made such observations on only one patient in whom a presumptive diagnosis of myelosclerosis was made. In her the length of the transfused cell was about thirty to forty days rather than the normal 120 days.

DR. ALEXANDER: Let us now take up another interesting aspect of this case, namely, the patient's cardiac failure. Dr. Smith, may chronic anemia *per se* give rise to cardiac failure?

DR. JOHN R. SMITH: Yes, anemia *per se* may precipitate cardiac failure. An analogous situation is not uncommon in patients with pernicious anemia, particularly those with some coronary artery sclerosis. They may develop angina when their red counts fall to low levels; and when their counts are restored to normal, they become free of angina.

DR. ALEXANDER: If a patient with an entirely normal heart develops prolonged chronic anemia, may heart failure develop?

DR. SMITH: I have not seen heart failure in patients whose hearts were presumably entirely normal before anemia occurred.

DR. ALEXANDER: Dr. Massie, do you have any comment?

DR. EDWARD MASSIE: I agree with Dr. Smith. One may demonstrate by the electrocardiogram as well as by clinical observation that coronary insufficiency develops in the presence of severe anemia in patients who have some underlying coronary disease and is completely controlled by restoration of the normal blood count. This patient had a number of electrocardiograms which were within normal limits. I take those records as evidence that he did not have serious coronary artery disease; otherwise, especially in view of his age, I would assume that in the presence of anemia as severe as he exhibited, electrocardiographic abnormalities would have been demonstrated.

DR. ALEXANDER: Is it true that chronic anemia results in an enlargement of the heart?

DR. MASSIE: Anemia, in my opinion, may lead to cardiac dilatation but I doubt that it leads to cardiac hypertrophy.

DR. WOOD: How does one tell?

DR. MASSIE: That statement was based on my own observations in several cases in which I thought cardiac hypertrophy had developed as a result of anemia; at autopsy no such hypertrophy was demonstrable and it was concluded that the hearts had merely been dilated.

DR. ALEXANDER: Do you believe that this patient's failure was due to underlying cardiac disease or to the anemia?

DR. MASSIE: If the patient had had an elevated venous pressure or particularly a prolonged circulation time, I would have favored a diagnosis of cardiac failure on the basis of primary cardiac disease. In the presence of anemia alone the circulation time should be short; therefore, if the circulation time were increased, I would favor primary cardiac disease.

DR. WOOD: I believe it is important to point out that in situations such as this one it is helpful to determine the venous pressure. I do not believe that anemia alone will cause the venous pressure to rise; if it is elevated, I would suspect that congestive heart failure is also present.

DR. ALEXANDER: Dr. Moore, have you seen organic changes in the heart as a result of prolonged anemia which lasted over a period of years?

DR. C. V. MOORE: I am not sure that I have seen real hypertrophy of the heart result, but I have certainly seen dilatation. Dr. Massie, if the cardiac muscle was involved extensively with extramedullary hematopoiesis, would electrocardiographic changes be demonstrable?

DR. MASSIE: If the infiltration consisted of only an isolated group of cells, the electrocardiogram would not be abnormal. On the other hand, if the focus was extensive, it might manifest itself by definite changes in the tracings.

DR. SAMUEL C. BUKANTZ: I should like to ask Dr. Smith how he would feel about the use of digitalis in the treatment of this type of heart failure.

DR. SMITH: In a patient such as this one with definite signs of cardiac decompensation I would certainly use a digitalis preparation.

DR. ALEXANDER: In summary I believe that we would certainly all agree that this patient had myelosclerosis with extramedullary hematopoiesis and that he had cardiac decompensation.

Clinical Diagnoses: Myelosclerosis with extramedullary hematopoiesis; leukemoid reaction; arteriosclerotic coronary artery

disease with cardiac failure; ? peripheral neuritis.

PATHOLOGIC DISCUSSION

DR. VERNON PETTIT: The skin and mucous membranes were pale and there was an extensive pitting edema of the subcutaneous tissues. In the peritoneal cavity there were 4,500 cc. of clear, amber fluid; 550 cc. of similar fluid were present in the left pleural cavity and 250 cc. in the right. The viscera contained little evidence of congestion. In the retropleural spaces along the lower five thoracic vertebrae there were dark red, circumscribed masses of tissue that were attached to the periosteum of the vertebrae and extended into prominent depressions in the bodies between the osteo-arthritic intervertebral joints. The masses extended laterally as far as 6 cm. and together they weighed 150 gm. On cut surface there were thin, fibrous trabeculae that divided the masses into indistinct lobules of dark red, meaty tissue. Similar tissue formed masses about the pancreas and extended into the hilus of the liver.

The spleen was greatly enlarged and weighed 1,150 gm. The capsule was thickened and the parenchyma firm, dark red and without visible follicles. The kidneys were enlarged due to the presence of dark grey tissue, similar to that along the vertebrae which filled the hilus of each kidney and extended inward around the major and minor calices. This tissue was firmly attached to the outer layer of the renal pelvis and extended for a short distance down each ureter. The renal substance itself was slightly decreased in amount and the kidneys contained anatomic changes of slight arteriolar nephrosclerosis. The femur was opened and had a markedly narrowed medullary cavity surrounded by a thickened layer of dense cortical bone. The marrow itself was firm and grossly fibrous. The vertebrae on cross section were very hard and almost solidly bone. The heart was enlarged to 350 gm. and there was moderate arteriosclerosis of the coronary arteries. Gross changes in the myocardium were not apparent.

DR. ROBERT A. MOORE: That this patient had osteosclerosis was evident from the gross appearance of the bones. There was a tremendous increase in the number of bony trabeculae in what should have been spongy bone. At the time of the autopsy we were much impressed with the masses in the retropleural spaces and about the kidneys, pancreas and hilum of the liver. Their gross appearance was very similar to that of some sarcomas and it appeared that they could have been due to primary tumor in the region of the pancreas with secondary extension and metastases to adjacent sites. Microscopic study, however, has proven this tissue to be of an entirely different type.

Figure 1 is of a section of bone which is typical of the bones throughout the body. The large number and great thickness of the trabeculae apparent at low magnification indicate tremendous proliferation of bone. Osteoid is present on the surfaces of these ramifying, irregular trabeculae. In addition, there is myelofibrosis; the bone marrow in many places is completely fibrotic although elsewhere there are a few cells of the normal bone marrow buried in the fibrous tissue. Figure 2 is a higher magnification of one of those areas to show that there are a few cells of the myeloid and erythroid series still present, but a great deal of this marrow has been replaced by fibrous tissue and bone. The myelofibrosis and osteosclerosis is a generally diffuse process, but microscopically there are small foci of well preserved bone marrow in most sections. There are, however, no areas that are clear of osteosclerosis.

Figure 3 is of a section of spleen which is extremely cellular and in which there are megakaryocytes scattered through the tissue. Cells of the myeloid and erythroid series comprise most of the cellular elements of the parenchyma. Figure 4 is of a section of one of the masses in the thorax. This structure was apparently a lymph node at one time as the capsule and peripheral sinusoid remain in some places. The greater

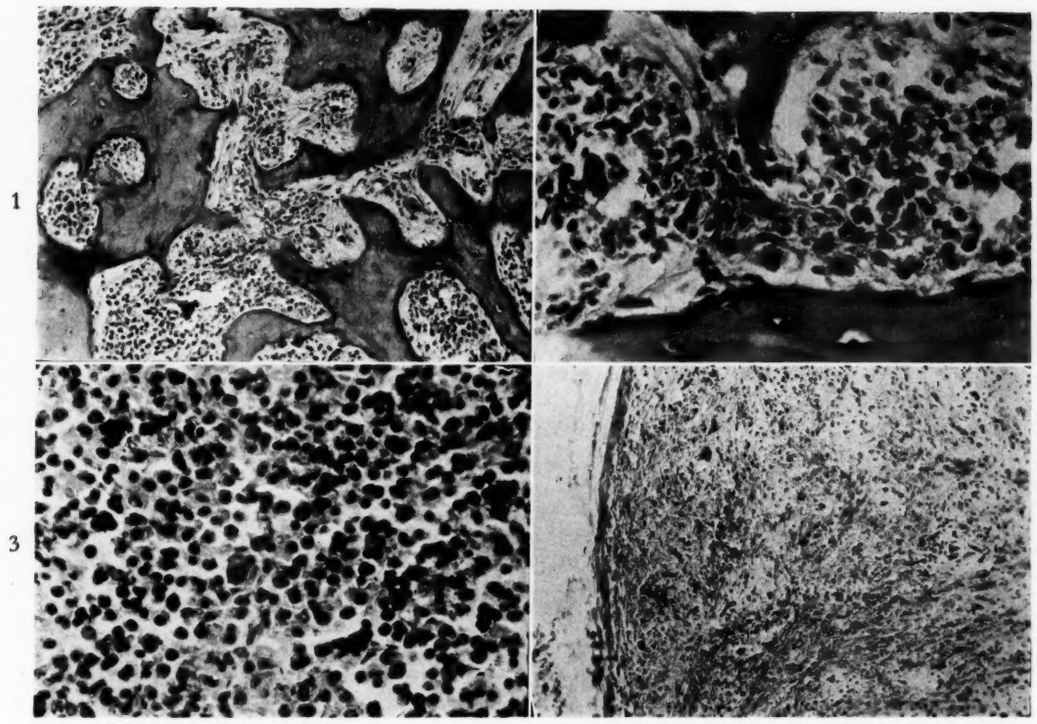

FIG. 1. A typical section of bone marrow with increased numbers of very large trabeculae lined by a layer of osteoid tissue. The remaining marrow is infiltrated and largely replaced by fibrous tissue.
FIG. 2. Myelopoietic and erythropoietic cells and the thickened trabeculae of the bone marrow at higher magnification.
FIG. 3. Extramedullary hematopoietic tissue that largely replaces the parenchyma of the spleen; the large, dark cells are megakaryocytes.
FIG. 4. A lymph node from the retropleural mass that is replaced by fibrotic extramedullary hematopoietic tissue.

part of the node has been destroyed and replaced by a loose type of connective tissue that has free cells scattered through it. Figure 5 is a higher magnification of one of the more cellular regions present in the node. It is clear that this lesion is not a sarcoma but that it represents extramedullary hematopoiesis. It is composed of cells of the myeloid and erythroid series in all stages of development. Many megakaryocytes are present here just as they were in the sections of the spleen. The great masses around the kidney and in the retroperitoneal areas about the pancreas and porta hepatis also consist of erythropoietic and myelopoietic tissue. Although the extramedullary hematopoiesis involves primarily the lymph nodes, it extends to other tissues as well. Not every lymph node is involved, however; sections of mesenteric lymph nodes, for example, contain no alteration whatsoever.

Figure 6 illustrates a section of the kidney from the region near the hilus. Tissue identical with that in the lymph nodes invades the perivascular trunkal tissue. This section shows clearly that the extramedullary hematopoietic tissue is not confined to the lymph nodes. Figure 7 is from the liver; there is an increased number of myeloid cells within the portal spaces and scattered through the sinusoids. Cells of the erythroid series can also be identified in this section. The section of heart (Figure 8) contains focal interstitial fibrosis with atrophy of the adjacent myocardial fibers. The small arteries and arterioles are thickened and sclerotic.

The central pathologic change in this case is myelofibrosis and osteosclerosis with extensive extramedullary hematopoiesis involving the liver, spleen, lymph nodes, retroperitoneal and retropleural tissues and the peripelvic and peritrunkal tissues of the

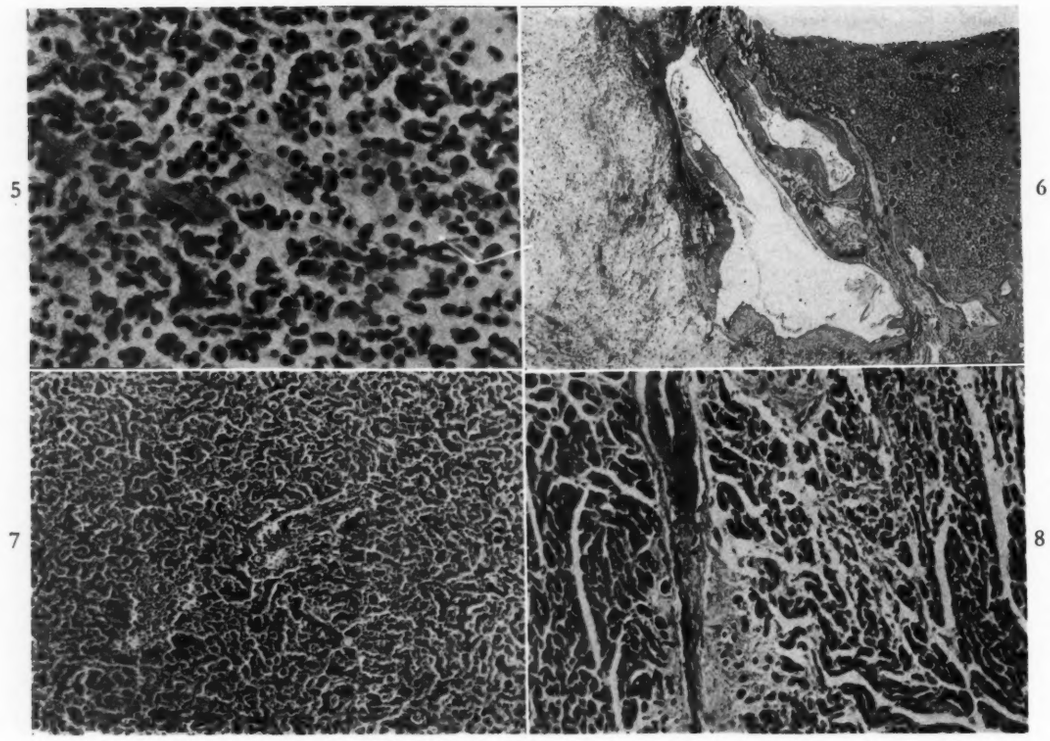

FIG. 5. A region of the more cellular portions of the hematopoietic masses beneath the pleura at higher magnification; note similarity to the section of the spleen.
FIG. 6. Topographic view of the fibrous hematopoietic tissue infiltrating along the vessels at the hilus of the kidney.
FIG. 7. Extramedullary hematopoiesis in the portal spaces and sinusoids of the liver.
FIG. 8. Focal interstitial fibrosis of the myocardium and arteriosclerotic thickening of a small artery in the myocardium.

kidney. Whether or not this is chronic myeloid leukemia or primary myelofibrosis with a leukemoid reaction is subject to some controversy. I think I could reasonably well defend either of these interpretations, but I must confess that I would defend the concept of leukemoid reaction and myelofibrosis with a good deal more enthusiasm than I would the diagnosis of chronic myeloid leukemia with a terminal stage of myelofibrosis and extramedullary hematopoiesis. The latter, however, has been cited throughout the literature as a possible explanation for such a case as this one. Although the hematopoietic tissue infiltrated the peripelvic tissue of the kidney and possibly eroded the vertebrae, I do not believe it was truly neoplastic. The mixed myeloid and erythroid nature of the cells is distinctly different from the infiltrating cells of the leukemias. Furthermore, in the liver there was not as much infiltration as in a typical example of chronic myeloid leukemia. No explanation of the etiology of the primary myelofibrosis and osteosclerosis is apparent.

The neurologic symptoms remain unexplained. The hematopoietic masses did not involve the nerve roots as far as we could determine at autopsy; and although they did involve the front of the bodies of the vertebrae, any resulting pain should have been referable to bone erosion rather than to nerve root involvement. In the brain we found a few petechiae and in one section a little focus of what appears to be extramedullary hematopoiesis. The spinal cord did not contain gross or microscopic lesions of combined system disease or other tract degenerations.

On the basis of the autopsy observations this patient's cardiac disease was independent of the disease of the bone marrow. The heart was hypertrophied and dilated in

comparison to the normal for a person of small stature such as this man was, and the degree of coronary arteriosclerosis and accumulation of fluid in the subcutaneous tissues and serous cavities suggested cardiac failure. There was no infiltration of the myocardium or fatty degeneration of the myocardium to suggest that the anemia might have had a significant influence. Certainly anemia, coming late in the course, may have been an added factor of strain to the coronary arteriosclerosis but the hypertrophy and dilatation of the heart in this instance cannot be attributed to long-standing anemia. Such does appear, at least according to autopsy observations, in not more than half of the patients with pernicious anemia where there may be fatty degeneration of the myocardium, dilatation supposedly due to the inadequate blood supply and hypertrophy resulting from the dilatation. That change, however, cannot be accurately correlated with the degree or duration of the anemia and is not recognized in other chronic severe anemias; so I am not inclined to attribute much importance to the anemia in this case as a cause of the cardiac failure.

Final Anatomic Diagnoses: Myelofibrosis and osteosclerosis; extramedullary hematopoiesis involving the tissues about the renal pelves, upper portions of the ureters and beneath the pleura along the vertebrae in the lower thoracic region, porta hepatis, the pancreas, liver, spleen, brain and peripancreatic and lesser omental lymph nodes; arteriolar nephrosclerosis, slight; hypertrophy and dilatation of the heart; arteriosclerosis of the aorta and splenic artery, advanced, and of the pulmonary, coronary and cerebral arteries, moderate; interstitial fibrosis of the myocardium.

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Special Feature

The Western Society for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE THIRD ANNUAL MEETING, SALT LAKE CITY, JANUARY 27 AND 28, 1950

INFLUENCE OF BLOOD GLUCOSE CONCENTRATIONS ON SERUM AMYLASE VALUES IN ACUTE PANCREATITIS; CLINICAL SIGNIFICANCE. *Reuben Straus, M.D. and (by invitation) Stella Mills.*, (From Temple Hospital, Beverly Hills, Calif.)

Although considerable fluctuation of serum amylase is said to occur normally, it is rare to find patients with proved acute pancreatitis without some elevation of serum amylase during at least part of the acute phase of the disease. The chance observation of a fluctuating reciprocal relationship between blood glucose concentration and serum amylase level in a patient with acute pancreatitis initiated this study.

Using the amylolytic technic of Somogyi the level of blood glucose and of serum amylase was studied in a series of patients with and without acute pancreatitis before, during and after intravenous administration of isotonic and hypertonic glucose and *in vitro*. Addition *in vitro* of concentrated glucose to blood from patients without pancreatitis produced a significant fall in the amylase level in six of the nine blood samples tested. In three diabetic patients with initially elevated blood glucose values the amylase levels were relatively low; but when the diabetes was brought under control the glucose levels fell and the amylase levels rose significantly. Of the eight patients with acute pancreatitis only two failed to maintain the reciprocal glucose-amylase relationship when glucose was injected intravenously.

Blood samples from the right and left ventricle of the heart of a patient who died from acute pancreatitis revealed the expected high glucose value in the right ventricle and a low glucose value in the left ventricle. The amylase level in the right ventricle was extremely low while that in the left ventricle was high.

This evidence indicates that some relationship does exist between the concentration of blood glucose and of amylase. The apparent reduction in the enzyme is not due to its destruction or utilization since reduction of the glucose level *in vitro* results in restoration of the former amylase levels.

AMINOPTERIN THERAPY IN ACUTE AND SUBACUTE LEUKEMIAS AND IN TERMINAL ACUTE EXACERBATIONS OF CHRONIC GRANULOCYTIC LEUKEMIA. *Arthur J. Seaman, M.D., Robert D. Koler, M.D., Thomas Stack, M.D. and Edwin E. Osgood, M.D., Portland, Ore. (Introduced by Norman David, M.D.)* (From the Division of Experimental Medicine, University of Oregon Medical School.)

Clinical and hematologic observations in sixteen aminopterin-treated patients with acute and subacute leukemias and terminal acute exacerbations of chronic granulocytic leukemia are presented. Additional therapeutic measures included blood transfusions, parenteral feedings and antibiotics whenever indicated.

Six of the sixteen patients experienced remissions, in some cases repeatedly. Toxic symptoms were frequent, sometimes severe, and often preceded conspicuous improvement by a few days. The need for day-to-day evaluation of dosage is emphasized.

Morphologic classification of all cases was possible and there were cases of monocytic, granulocytic, and lymphocytic types of leukemia who responded to aminopterin therapy and cases of each of these types who failed to respond. Aminopterin-induced remissions occurred in approximately half of the children with acute leukemias and approximately one-third of the adults with acute and subacute leukemias, sometimes repeatedly. Aminopterin failed to alter the rapid downhill course of three patients with terminal acute exacerbations of chronic granulocytic leukemia.

DISAPPEARANCE OF LEUKEMIC CELLS IN NON-LEUKEMIC RECIPIENTS DURING TRANSFUSIONS AND CROSS-CIRCULATION STUDIES.

Howard R. Bierman, M.D., R. L. Byron, Jr., M.D., (by invitation) Jonathan T. Lanman, M.D. (by invitation) and Patrice L. Morrow, M.S. (by invitation). San Francisco, Calif. (From the Laboratory of Experimental Oncology, University of California Medical School.)

Rapid transfusion of 9 to 120 billion leukemic leukocytes into non-leukemic subjects revealed that the leukemic leukocytes fail to appear on the arterial side of the lesser circulation. Heparinization permits leukemic cells to pass the usual removal mechanism in the lungs.

By developing a method of direct artery-to-artery cross circulation in man an attempt was made to filter out leukemic cells in leukemic patients in the lung filter of non-leukemic patients. It is possible to cross-transfuse 6 to 10 L. of blood per hour both to and from the donor and recipient. To date 80 L. of blood have been cross-transfused within a thirteen-hour period. Marked decreases in leukocyte counts in the leukemic patients were observed some hours following cross transfusions. Leukemic skin infiltrations disappeared overnight and clinical improvement was noted within an hour after the cross circulation was begun. No evidence of leukemia has been detected in any recipient. Postmortem studies showed degenerating leukocytes and absence of leukemic infiltration of the liver, spleen and bone marrow of the leukemic patients.

The concept that an impaired removal mechanism may be as important as proliferation in leukemia has been strengthened.

ANEMIA OF INFECTION: CLINICAL EXPERIENCES WITH FERRIVENIN. *William J. Kuhns, M.D. (by invitation), George E. Cartwright, M.D. and Maxwell M. Wintrobe, M.D. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

The anemia of infection is characterized by impaired hemoglobin synthesis which occurs despite administration of more than adequate quantities of iron. The reason for this is not understood, although it is frequently assumed that iron diversion occurs possibly for a purpose concerned in the response to the infection. In the present study the effects of huge amounts (from 1.0 to 2.2 gm.) of intravenously administered saccharated oxide of iron (Ferrivenin) were observed in ten patients who manifested the anemia and/or hypoferremia of infection. Methods of study included determination of baseline hematocrit, hemoglobin, corpuscular indices, reticulocytes and serum iron, followed by frequent similar determinations during and after the period of iron administration.

Despite the large doses given in no instance was the hypoferremia corrected. In a few cases there was a suggestive hemoglobin rise although in no patient was there an adequate reticulocytosis. In no case was there a hemoglobin rise or reticulocytosis comparable to that obtained in iron-deficiency anemia. Strict comparisons between both conditions were rendered difficult because (1) the degree of anemia associated with infection was often not comparable in degree with the iron-deficiency anemia and (2) evaluation of hemoglobin increases was frequently complicated by subsidence of the infection. However, follow-ups during the infection were generally sufficiently prolonged (four to six weeks after beginning iron therapy) to indicate that hemoglobin synthesis is slow and sometimes apparently does not occur during infection, whereas synthesis is rapid and relatively prompt in iron-deficiency anemia. The results suggest that the anemia and hypoferremia of infection are not appreciably benefited by the intravenous administration of large quantities of iron.

Studies on urinary iron excretion in two patients indicated that from 3 to 7 per cent of the iron administered is excreted by this means. Iron analyses on viscera obtained from a treated patient who subsequently died showed that approximately three-fourths of the iron is recoverable in the liver.

VASODEPRESSION BY IRON AND ITS REVERSAL BY RUTIN. *Jefferson M. Crismon, M.D. Stanford, Calif.* (From the Department of Physiology, Stanford University School of Medicine.)

The hepatic vasodepressor material (VDM) was recently identified as ferritin (Mazur and Shorr.) Vasodepression was attributed to the protein, apoferritin; the possibility of intravascular addition of iron to apoferritin was not excluded.

Possible vasodepressor actions of iron were studied by means of the Chambers-Zweifach rat mesoappendix technic. Ferrous sulfate in distilled water was injected intravenously into test rats after initial epinephrine thresholds were

determined. Doses calculated as Fe^{++} were based upon the amount of iron necessary to saturate the iron-carrying globulins of plasma. Laurell and others have reported toxic effects of iron crystalloids if "saturation limits" are exceeded.

After intravenous injection of 91 micrograms per kg. body weight of Fe^{++}, topical application of epinephrine solutions 2 to 5 times as concentrated as those used in the pre-injection test were required to produce contraction of precapillary sphincters. Depression appeared in two to ten minutes and was maximal in twenty to forty minutes. Injections of similar volumes (0.1 ml. per 100 gm. body weight) of distilled water produced slight increases in sensitivity to epinephrine. Larger amounts of ferrous sulfate, 2 to 4 times the "saturating dose," produced signs of respiratory distress. Greatly increased sensitivity of precapillary sphincters to epinephrine was observed but could not be differentiated from typical asphyxial responses described by Zweifach.

Rutin in doses of 2 mg. per kg. intravenously restored epinephrine sensitivity after its depression by iron. Similar reversal by rutin of vasodepression produced by VDM from anaerobically incubated liver and by post-tourniquet edema fluid was also demonstrated.

Iron furnished as a protein complex or as Fe^{++} reduces terminal vascular responses to epinephrine. Prompt restoration of epinephrine sensitivity is accomplished by rutin, a substance having no direct vasotropic action. The possible role of iron as an essential part of epinephrine-destroying enzymes and that of rutin as a competitive inhibitor, acting by chelate association with iron, are under investigation.

TITERS OF HETEROPHILE ANTIBODIES AND OF ANTISTREPTOLYSIN "O" IN ACUTE GLOMERULAR NEPHRITIS AND IN THE NEPHROTIC SYNDROME. *David A. Rytand, M.D. and (by invitation) Elizabeth Randall, M.A. San Francisco, Calif.* (From the Department of Medicine, Stanford University School of Medicine.)

Titers of heterophile agglutinins and of antistreptolysin "O" were determined by standard methods in sera obtained from forty-three children and adults with the nephrotic syndrome and twenty-six with the initial stage of glomerular nephritis (non-nephrotic). In most patients only a single pair of determinations was possible.

The antistreptolysin titer was 12 units per ml. or less in all but six patients with the nephrotic syndrome; the exceptions were twenty-one to forty years of age. In initial glomerular nephritis the antistreptolysin titer was only 166 or less in nine patients aged eleven to forty but was otherwise 250 or greater. Heterophile agglutinins, shown by Raffel to resemble those found in normal sera, were slightly elevated in titer in a few instances of glomerular nephritis especially under thirty years. More striking but only moderate elevations of titer were found in the nephrotic syndrome in patients as old as sixty but not older; greater increases (112–224) were observed in this syndrome especially before the age of five. Particularly in the group aged one to ten there seemed to be an inverse relationship between the two antibodies.

In one subject without renal disease a low antistreptolysin titer and increased heterophile agglutinins were discovered accidentally shortly before the onset of the nephrotic syndrome, with similar findings in two others after healing. Preliminary observations with L. A. Rantz indicate the presence in the urine of antistreptolysin in amounts inadequate to account for the low serum titer characteristic of nephrotic syndrome.

The findings appear to represent exaggerations of the titers of these antibodies reported in "healthy" individuals at certain age groups; they are compatible with the known age incidences of the two manifestations of Bright's disease and may perhaps serve at least partially to characterize the immunologic constitution of patients in whom these disorders occur.

CHEMICAL ESTIMATION OF ALPHA GLOBULIN IN HUMAN SERUM. ITS POSSIBLE RELATION TO THE HUGGINS' TEST FOR CANCER. *B. V. Jager, M.D. and (by invitation) Margaret Nickerson. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

Serum alpha globulin was determined chemically by a differential salting-out method, by estimation of total serum polysaccharide according to the method of Seibert and by estimation of serum mucoprotein with the technic of Winzler. Various alterations were made in the sera of patients in whom the thermocoagulability of the serum had been determined with the Huggins' test in order to discover what factors would vary the results.

Each of the three chemical methods for alpha globulin estimation was found to have definite limitations when regarded as an index of alpha globulin as determined electrophoretically. However, in general, agreement was good. As has been observed by others, the degree of increase of alpha globulin in sera usually is proportional to the severity of active tissue destruction. Nonetheless many exceptions occur. In nearly all instances in which a positive Huggins' test for cancer was obtained, the alpha globulin content was found to be greatly increased. Certain other factors that may be significant in the mechanism of production of a positive Huggins' test were observed.

STUDIES ON THE RELATION OF DIET, CHOLESTEROL AND ATHEROMA IN CHICKENS. *John E. Peterson, M.D. and (by invitation) Albert E. Hirst, M.D. Loma Linda, Calif.* (From the School of Medicine of the College of Medical Evangelists.)

The similarity between human atherosclerosis and that occurring spontaneously in chickens has been noted by several workers. It also has been shown that cholesterol feeding will greatly hasten the development of atheromatous lesions in young chickens. This report concerns observations made in a hundred cockerels fed diets of varying content. At the outset one group of twenty-five chicks was placed on a normal mash diet for control. Another group of twenty-five was fed mash with added vegetable fat—cotton seed oil. A third group of twenty-five was fed mash with added animal fat—lard. A fourth group of twenty-five was fed mash with added cholesterol dissolved in cotton seed oil. As soon as the feeding program was well established, birds from each group were autopsied and the various organs, including the heart and vascular system, were subjected to gross and microscopic examination.

As expected from previous studies, severe atherosclerosis developed rapidly in the cholesterol-fed birds. There was no significant difference between the cotton seed oil- and the lard-fed birds. Although there was some difference in growth, general appearance and behavior between the controls and the birds on a high-fat diet, the latter showed no appreciable increase in atherosclerosis.

When atheromatosis was well developed in the cholesterol-fed chicks, three cockerels were withdrawn from the group and underfed. Later three more were withdrawn. Observations in these birds suggest that there is rapid and spontaneous reversal of atheroma produced by cholesterol feeding if cholesterol is withdrawn from the diet in time. If hypercholesterolemia is prolonged, however, there may be a point beyond which lesions are irreversible.

NUMBER AND SIZE OF FAT GLOBULES (LYPOMICRONS) IN THE CIRCULATING BLOOD IN NORMAL INDIVIDUALS AND IN PATIENTS WITH CORONARY DISEASE. *Willard J. Zinn, M.D. (by invitation) and George C. Griffith, M.D. Los Angeles, Calif.* (From the Department of Cardiology, University of Southern California School of Medicine.)

The immediate problem has been to determine whether or not large fat droplets in the serum (chylo-microns) and their relationship to the total number of fat droplets (lypomicrons) show any significant relationship to atheromatous disease in man. The initial method consisted of the following procedure: (1) Fasting capillary blood serum separated by mild centrifugation obtained from patients with coronary occlusion or history of coronary occlusion, diabetic patients and normal controls all over the age of fifty. (2) Study of the entire serum sample under darkfield microscopic examination. (3) Estimation by the use of a net micrometer of the total fat particles and the total large fat particles.

In ten normal adult males, ranging from fifty to ninety-six years of age without evidence of heart disease in the family, the ratio of chylomicrons to lypo-microns ranged from 0.22 to 0.37. In eight diabetic patients with evidence of atherosclerotic disease the range was from 0.46 to 0.78. In seven male patients with old or recent myocardial infarctions the fasting ratio ranged from 0.48 to 1.0.

Although the selected cases are still few in number there is an apparent suggestion of a relationship between the proportion of large particles and the tendency to atheromatous disease.

PRODUCTION OF ARTERIAL HYPERTENSION IN THE RAT BY SUBSTITUTION OF HYPERTONIC SODIUM CHLORIDE SOLUTIONS FOR DRINKING WATER. *Leo A. Sapirstein, Ph.D., M.D. (by invitation), Wilbur L. Brandt, M.S. (by invitation) and Douglas R. Drury, M.D.*

Los Angeles, Calif. (From the University of Southern California.)

A disturbance in the metabolism of salt and water in animals made hypertensive by the Goldblatt technic and its modifications and in essential hypertension may be inferred from a considerable body of recent work. The possibility that this disturbance can be duplicated and hypertension induced by presenting animals with sodium chloride solutions in concentrations sufficient to tax the regulatory functions of the kidney is the subject of the present communication.

Fifty-eight adult rats were used in three experiments. The experimental animals received a 2 per cent sodium chloride solution as the sole source of drinking water. Control animals received tap water. Systolic blood pressures were measured by tail plethysmography during a control period and for six weeks after instituting the sodium chloride solutions. Systolic pressures of control animals averaged 101 mm. Hg with a standard deviation of 4. The animals receiving sodium chloride showed a mean systolic pressure of 132 mm. Hg with a standard deviation of 13. The heart weight/body weight in the control animals was .307 per cent, with a standard deviation of .024; in the experimental animals this ratio was .386 with a standard deviation of .036. These differences are statistically significant.

These results, taken in conjunction with the findings of others who have been unable to produce hypertension in animals or men on high salt diets when water intake is not restricted, indicate that the ratio of sodium chloride to water intake rather than the sodium chloride intake alone is the determining factor in the development of this type of hypertension.

PROTECTIVE AGENTS FOR EPINEPHRINE CYCLOPROPANE-INDUCED CARDIAC ARRHYTHMIAS. *E. L. McCawley, Ph.D. and J. M. White, M.D.* (*introduced by N. A. David, M.D.*). *Portland, Ore.* (From the Departments of Pharmacology, the Schools of Medicine, University of Oregon and Yale University.)

Despite the advantages of ease of induction and low degree of physiologic insult with cyclopropane anesthesia, action on the heart limits its use in certain branches of surgery. Under cyclopropane anesthesia surgical manipulations, especially of the heart and great vessels, set off episodes of ventricular premature contractions, ventricular tachycardia and occasionally ventricular fibrillation. The use of procaine is effective in combatting most of these arrhythmias (Burnstein. *Anesthesiology*, 7: 113, 1946). When the dog is anesthetized with cyclopropane, no arrhythmias develop until epinephrine (adrenalin) is injected. As the ventricular tachycardia may thus be produced at will, the protective value of any drug against these arrhythmias may easily be studied.

Single doses of procaine (10 to 15 mg./kg.) provide complete protection against these arrhythmias. Other local anesthetics, metycaine, tetracaine or nupercaine, do not afford any protection. These latter local anesthetics are all more potent than procaine but also considerably more toxic; dosages of 10 to 20 mg./kg. were fatal.

Brodie has shown that procaine is rapidly hydrolyzed by a plasma enzyme, forming para-aminobenzoic acid and diethylaminoethanol. The two split products were then tested and only the alkaminoethanol was found capable of preventing the epinephrine cyclopropane arrhythmias. Its effective dose is 225 to 300 mg./kg. Thus substitution on the oxygen atom of diethylaminoethanol would appear to increase its effectiveness 20 to 30 times. The spasmolytic drug, trasentin, which is also an alkaminoethanol ester, was found to be a protecting agent at the same dose level as procaine (10 mg./kg.). Antiarrhythmic activity was found in another pharmacologic class, the antihistaminics. Benadryl, an alkaminoethanol ether, provides protection at 5 to 10 mg./kg. Ethyl ether itself has a surprisingly powerful protective action. Other antihistaminics in which the oxygen of the diethylaminoethanol is replaced by nitrogen are ineffective at any dosage level.

CATHERIZATION ARRHYTHMIAS. *J. Michel, M.D., A. D. Johnson, M.D., W. C. Bridges, M.D., J. H. Lehman, M.D., F. Grey, M.D., L. Field, M.D.* (*by invitation*) *and D. M. Green, M.D. Chicago, Ill.*

The incidence of arrhythmias was analyzed in a series of 133 consecutive venocardiac catherizations. Abnormal rhythms developed in more than one-third of the group. The tendency was significantly greater in the presence of congenital heart lesions and in patients whose electrocardiograms were abnormal prior to the procedure. Age, sex, heart rate and blood pres-

sure were not shown to influence the incidence.

All but two of the arrhythmias subsided during or immediately following the catherization. One instance of intraventricular block persisted for more than four hours. One other patient, in whom anesthetic respiratory depression was present, developed a series of arrhythmias which persisted and appeared to contribute to the ultimately fatal outcome.

Direct stimulation of the endocardium by the catheter appeared to be responsible for the majority of the arrhythmias. A number, however, seemed explicable only on the basis of reflex excitation of foci of impulse formation.

POTENTIAL VARIATIONS OF THE EPICARDIAL AND ENDOCARDIAL SURFACES IN ANOMALOUS ATRIO-VENTRICULAR EXCITATION. *Hans H. Hecht, M.D. and (by invitation) Leonard Ritzmann, M.D. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

The potential variations of the thorax and esophagus in ten cases displaying anomalous atrio-ventricular excitation (WPW syndrome) have been analyzed in a previous report (Rosenbaum, Hecht, Wilson and Johnston: *Am. Heart J.*, 29: 281, 1945). To this group six new cases are added in all of whom multiple right- and left-sided precordial leads, backleads and leads from the esophagus were obtained. In four of the six subjects potential variations were also recorded from the right auricular and ventricular cavities. Displacement of the pacemaker from the sinus region into the lower part of the a.v. junction was accomplished in five subjects by reflex vagal stimulation following the intravenous administration of 1 mg. of neosynephrine.

Normal ventricular complexes occurred once spontaneously in four others following the artificial shift in cardiac pacemaker to lower auricular centers. As in the previous series the distance from P to peak of R was identical in the normal and abnormal complexes. High esophageal leads and leads V_R usually displayed extremely short P-R intervals and deep Q-S deflections. Endocardial electrocardiograms displayed significant R waves if the right precordial leads were abnormal ("group A"), deep Q-S deflection or Qr deflection were noted in the remainder ("group B"). Transitional complexes occurred frequently.

In one instance the degree of pre-excitation increased sharply as the electrode was removed toward the tricuspid region and varied from 0.08 sec. to 0.13 sec. in width within the same ventricle.

The results lend further support to the assumption that in the WPW syndrome certain sections of ventricular muscle are activated prematurely and that the main body of ventricular muscle responds to the same impulse conducted over the regular pathways. Anomalous atrio-ventricular excitation represents an instance of "double excitation" with the abnormal pathway presumably facilitating pre-excitation of muscle sections of the base of both right and left ventricles. It is likely that the abnormal pathways traverse the posterior portion of the septum in the majority of cases, and that the degree of pre-excitation of basilar sections of one ventricle as compared to the other determines the two types of the syndrome (A and B) previously described.

NATURE OF AURICULAR FIBRILLATION. *Robert Oblath, M.D. (by invitation), Eliot Corday, M.D. (by invitation), Isidor C. Brill, M.D. (by invitation) and Myron Prinzmetal, M.D. Los Angeles, Calif.* (From the University of California and Cedars of Lebanon Hospital.)

The present theory of the mechanism of auricular fibrillation is that this disturbance consists of an irregular circus movement with an excitable gap between the head and tail of the wave. The gap should be represented electrocardiographically by an isoelectric period. Because the cathode-ray oscillograph faithfully records electrical impulses in frequency ranges far beyond the scope of the ordinary electrocardiograph, oscillographic tracings were obtained from the auricles in dogs and from esophageal leads in man during auricular fibrillation. A dual-beam cathode-ray tube oscillograph was used; records were made on continuous strip films with the film speed utilized as the time base.

Examination of the records reveals that there is complex auricular activity of at least two types: (1) very minute rapid waves and (2) large relatively rhythmic slower waves of constantly varying configuration. It was found that there is continuous electrical activity; at no time is there an isoelectric period. Thus there is no evidence of an excitable gap.

Simultaneous records from two closely adjacent unipolar electrodes placed at numerous selected points on the auricular surfaces show that the waves are arrhythmic and unrelated in frequency or amplitude. There is no evidence of a circus movement.

Records made through esophageal leads in man with auricular fibrillation demonstrate electrical activity identical with that found in the experimental animal.

It was shown that digitalis greatly reduces both the amplitude and frequency of all types of electrical activity in the fibrillating auricles. The decreased electrical bombardment of the auriculo-ventricular node offers an explanation for the decreased ventricular rate in auricular fibrillation after digitalis administration.

It is concluded that in both man and animals auricular fibrillation is a chaotic heterorhythmic disturbance. There is no circus movement.

RANGE OF ELECTRICAL CURRENTS WHICH WILL PRODUCE AND STOP FIBRILLATION IN DOGS. *Sanford E. Leeds, M.D., R. Stuart MacKay, Ph.D. (by invitation) and Kenneth E. Mooslin, M.D. (by invitation). San Francisco, Calif.* (From the Harold Brunn Institute for Cardiovascular Research, Mt. Zion Hospital.)

In order to construct a serviceable defibrillator for use in patients requiring cardiac surgery, an investigation to determine the optimum current for this purpose was undertaken. A timing circuit was developed which permitted the use of currents of durations from 0.01 to 6.0 seconds and voltages roughly from 4 to 300. This device and its special properties have been described in a separate paper. A double-channel oscillograph was employed to record simultaneously the voltage applied across the heart and the amperage. By this means the resistance of the heart during the passage of the current could be calculated.

The results indicate that there is a mid-zone of amperage at which both defibrillation and fibrillation can occur in the same animal. It was also shown that the resistance of the heart changes as the current passes through it. Observations on the effects of quinidine given preoperatively on the susceptibility of the heart to the production of fibrillation and the ease of defibrillation were made.

A STUDY OF UNIPOLAR PRECORDIAL AND LIMB LEAD ELECTROCARDIOGRAMS IN CONGENITAL HEART DISEASE. *Maurice Sokolow, M.D. and (by invitation) Archie L. Edgar, M.D. San Francisco, Calif.* (From the Division of Medicine, University of California Medical School.)

Ventricular hypertrophy is a helpful diagnostic sign in congenital heart disease but the radiologic methods of determining its presence in infants and children have been notoriously unsatisfactory. Therefore, complete twelve-lead unipolar electrocardiograms were obtained in 116 patients with various types of congenital heart disease. Thirty of the cases were studied at autopsy.

In thirty-four patients with tetralogy of Fallot, all but one showed typical right ventricular hypertrophy; one (a three and one-half month old infant) had right bundle branch block. In no case was the record normal nor did any show left ventricular hypertrophy. Right ventricular hypertrophy was also found in twenty-four patients with miscellaneous cyanotic cardiac lesions with the exception of five whose records demonstrated left ventricular hypertrophy or left axis deviation. Of these five, two patients had tricuspid atresia with non-functioning right ventricle and pulmonary stenosis; one, a truncus arteriosus; and two, pulmonary stenosis with associated patent ductus arteriosus.

In the acyanotic group unipolar electrocardiograms in thirty-three cases of uncomplicated patent ductus arteriosus were normal in seventeen patients, showed left ventricular hypertrophy in fifteen and incomplete right bundle branch block in one. In no case of uncomplicated patent ductus was the pattern of right ventricular hypertrophy obtained. There was an excellent correlation between the size of the ductus and the electrocardiogram in that the ductus never exceeded 1 cm. in diameter when the electrocardiogram was normal. There were twenty-four cases of coarctation of the aorta; five of these patients had normal records; fourteen revealed left ventricular hypertrophy; three showed right ventricular hypertrophy (all with either cardiac failure and a patent foramen ovale or other associated congenital defects); and two had right bundle branch block in addition to left ventricular hypertrophy.

In the thirty autopsied patients, all those in whom an electrocardiographic diagnosis of right or left ventricular hypertrophy was made demonstrated this abnormality at autopsy. Only

one patient with major hypertrophy of a ventricle at autopsy was not diagnosed from the the electrocardiogram. He had combined hypertrophy with a right ventricle of 1 cm. in thickness. The electrocardiogram showed right axis deviation but no clear evidence of ventricular hypertrophy.

The exceedingly high diagnostic accuracy of the electrocardiographic patterns in ventricular hypertrophy should prove of definite value in the diagnosis of a suspected case of congenital heart disease.

EFFECT OF EXERCISE ON VENOUS PRESSURE OF PATIENTS WITH HEART DISEASE IN THE ABSENCE OF INCREASED BLOOD VOLUME. *Jack D. Lange, M.D. (by invitation), Benjamin Shorr, M.D. (by invitation), James Hopper, Jr., M.D. and Ellen Brown, M.D. San Francisco, Calif.* (From the University of California School of Medicine.)

Experiments were designed to determine whether the abnormal response of the venous pressure to exercise which has been observed previously in cardiac failure is dependent on a large blood volume or may be related to other factors. Eight patients with various forms of heart disease in whom signs of frank congestive failure were absent, fourteen healthy males in the basal state and 3 healthy males who had been rendered plethoric by salt and water ingestion were subjected to five-minute periods of exercise in a recumbent position, using a weighted treadle, the external work performed totalling approximately 3,500 to 6,000 foot pounds. Blood volume was measured with carbon monoxide and T-1824 prior to exercise. Venous pressure was measured by saline manometer. Heart rates were recorded electrocardiographically. Respiratory rates and qualitative records of excursion and position of the rib cage were recorded pneumographically.

Blood volume was not greater than the predicted normal in any patient. An inspiratory chest position was assumed during exercise by almost all subjects; depth of respiration increased in only five patients and one control. Resting venous pressure was normal in all subjects. In normal individuals venous pressure rose during exercise but fell to resting or below within thirty seconds after cessation of exercise.

In most cardiac patients the venous pressure curves were similar in general appearance to those of the normal subjects, but in three patients the elevation of pressure during exercise was considerably greater and more sustained, and in two patients recovery was delayed. In three normal subjects, who were plethoric because of salt and water ingestion, resting venous pressure was higher and the rise during exercise greater than in their own control experiments.

These results appear to show that an abnormal venous pressure response to exercise may occur in certain patients with myocardial insufficiency in whom blood volume is not increased but that the differences between such patients and normal individuals are slight.

ELECTROLYTE PROBLEMS IN THE SURGICAL PATIENT, WITH PARTICULAR REFERENCE TO SERUM CALCIUM, MAGNESIUM AND POTASSIUM LEVELS. *Helen Eastman Martin, M.D., Hugh Edmondson, M.D., Ralph Homann, M.D. (by invitation) and C. J. Berne, M.D. (by invitation). Los Angeles, Calif.* (From the University of Southern California School of Medicine.)

Serial determinations of serum calcium, magnesium and potassium levels were performed in six patients with nasogastric suction who were receiving only intravenous fluids. A drop in the serum calcium, magnesium and potassium levels occurred in each patient. In one of these patients the fall of serum calcium and magnesium was marked and was associated with the development of severe tetany. In another the serum calcium and magnesium levels were very low but there were no symptoms of tetany. A complete electrolyte and nitrogen balance study was performed in one patient. The cause of the fall in serum calcium was not completely elucidated by this study. The change in the serum magnesium level could be related in part to loss in the urine during the period when the intake was minimal or nil.

Serum potassium determinations in over 100 surgical patients had suggested that several conditions were frequently associated with potassium deficits and potassium loss from the body. These conditions included alkalosis, prolonged nasogastric suction, prolonged use of parenteral fluids without potassium and intestinal fistulas or diarrhea. Potassium balance studies in the six patients, who are the subject of this report, showed that the fall in serum level was due to continued urinary loss in the presence of inadequate intake. Symptoms and signs referable to severe potassium deficits were

present in the skeletal muscles (soreness, weakness or paralysis of muscles), the cardiovascular system (cardiac dilatation, tachycardias, gallop rhythms) and the gastrointestinal tract (ileus).

Correlation of urine chloride excretion with serum chloride level, as a gauge for the prevention of alkalosis, was made in several patients. These studies showed that the urine chloride test was not always a reliable means of detecting plasma chloride deficits.

These studies indicate the need for prophylactic use of repair fluids containing all electrolytes which may be lost from the body during periods of prolonged intravenous therapy.

CORRELATION OF THE ANALGESIC RESPONSE TO NITROUS OXIDE AND NITROUS OXIDE-AMPHETAMINE WITH PERSONALITY FACTORS. *Janice Norton, B.A. (by invitation), Mark Nickerson, Ph.D. and Agnes M. Plenk, M.A. (by invitation). Salt Lake City, Utah.* (From the Departments of Pharmacology and Psychiatry, University of Utah College of Medicine.)

Wide individual variations in the response of patients to analgesic agents are frequently encountered but the basis for this is poorly understood. The role of depression of higher levels of the central nervous system in the production of N_2O analgesia, and the frequent appearance of behavior characteristic of release from cortical inhibition in patients receiving this agent suggested that personality factors might be of particular importance in modifying its effect.

In an effort to evaluate the significance of personality in altering the response to analgesic concentrations of N_2O, nine medical students were subjected to Rorschach testing and were ranked on the basis of six factors: (1) conformity, (2) anxiety, (3) ego strength, (4) introversion, (5) emotional control and (6) hostility. Pain thresholds were determined on the same individuals by two methods: (1) the time required for deep pain to develop in a hand placed in water at 4°C. after equilibration at 30°C. and (2) the Hardy-Wolff-Goodell radiant heat technic for cutaneous pain. After studies of control thresholds, responses to N_2O (33 per cent in O_2 by face mask) with or without dextro-amphetamine (10 mg. orally) were determined.

High absolute pain threshold was found to be positively correlated with introversion, hostility and relatively low emotional control. In addition, individuals with a high emotional tension (the most anxious, hostile and conforming) responded to N_2O with the greatest rise in threshold. Their analgesic response was also less completely antagonized by amphetamine than was that of other members of the group.

These observations indicate that N_2O analgesia is associated with a generalized release of emotional tension. Individuals with high components of psychic factors indicative of tension receive the greatest analgesic effect from the agent, tend to maintain this analgesia in spite of amphetamine antagonism and appear to be the most likely to exhibit bizarre behavior while under its influence.

PERSONALITY PROFILES IN PATIENTS WITH ESSENTIAL HYPERTENSION. *Robert E. Harris, Ph.D. (by invitation) and Maurice Sokolow, M.D. San Francisco, Calif.* (From the Divisions of Psychiatry and Medicine, University of California Medical School.)

Clinical psychiatric studies of patients with essential hypertension have provided a number of hypotheses concerning the possible contribution of psychogenic factors to the disease process. Critical tests of the validity of these hypotheses are difficult to design because of the inherent subjectivity and lack of control in the clinical interview. Objective personality measures derived from the Minnesota Multiphasic Personality Inventory allow for the elimination of subjective factors, the influence of preconceived hypotheses, etc., and for a critical test of some of the hypotheses suggested by the clinical psychiatric data.

Personality inventories were obtained on eighty patients with essential hypertension. These profiles were contrasted with those obtained from normals, patients with duodenal ulcers and patients convalescing from a variety of physical diseases, operations, accidents, etc. Group averages, group profiles and individual profiles were analyzed for deviation from normality and for characteristic kinds of defenses against anxiety.

More than three-fourths of the hypertensive records were abnormal and significant differences from the other patient groups were obtained. In general the hypotheses derived from clinical psychiatric interviews were confirmed. Personality characteristics include overly rigid defenses and difficulties in the control of hostile impulses. A full description of the patients

oriented toward possible psychotherapeutic approaches will be attempted.

APPLICATIONS OF CINEFLUOROGRAPHY TO RESEARCH AND DIAGNOSIS. *Robert F. Rushmer, M.D. Seattle, Wash.* (From the Department of Physiology and Biophysics, University of Washington.)

Motion picture photography of the images on a fluorescent screen offers diverse opportunities for recording activity of internal organs. During the past two years this technic has been used to study the changes in the cardiac silhouette produced by contraction of the heart, respiratory activity and rotation of the patient into the oblique positions. Practical utilization of cinematic fluorography for recording angiocardiography has been demonstrated on dogs and in one case with congenital heart disease. The fluoroscopic appearance of congenital hearts is being permanently recorded on motion picture film. The projected images reveal greater contrast and more detail than is available during routine fluoroscopy.

Additional films have been produced which illustrate movements in various joints. The action of the anconeus muscle in pronation and supination of the forearm has been studied by this method in collaboration with Drs. Johnson and Ray. Mastication and deglutition have also been photographed.

TREATMENT OF AMEBIC COLITIS WITH AUREOMYCIN. *John F. Waldo, M.D. (Introduced by Hans. H. Hecht, M.D.) Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

In June, 1949, McVay, Laird and Sprunt reported a very small series of cases indicating that aureomycin appeared to be an effective agent in the treatment of intestinal amebiasis. Because this would be a very simple treatment for this disease and one requiring only a short period of treatment, it seemed well to repeat this experiment on a larger group of cases. It also seemed of interest to follow in some ways the bacterial flora of the stool to see if any possible relationship between disappearance of amebas and alteration of bacterial flora could be demonstrated.

To date five patients with intestinal amebiasis have been treated with aureomycin. Four had an uneventful course; amebas disappeared from the stools and all symptoms cleared. The fifth patient had very severe dysentery, with an average of twenty bloody stools a day. When aureomycin was administered, his symptoms ameliorated; amebas disappeared from the stools but the bloody diarrhea continued although it diminished somewhat. After five days symptoms recurred although no amebas were found in the stools.

To date the bacteriologic data have shown no significant or consistent alteration but studies are incomplete. It would appear that aureomycin has a direct amebacidal effect and is a useful form of therapy. Investigation of its therapeutic effectiveness is continuing and additional patients are being treated at this time.

STUDIES ON THE ANTIBODIES AGAINST MUMPS VIRUS IN MOTHER AND NEWBORN. *Henry B. Bruyn, M.D., Beatrice England and Edwin H. Lennette, M.D. (Introduced by Henry Brainerd, M.D.) San Francisco and Berkeley, Calif.* (From the Infectious Disease Laboratory of the San Francisco County Hospital.)

Quantitative studies on the placental transfer of complement-fixation and agglutination-inhibition antibodies against mumps virus have not been reported. Four cases of mumps, occurring in mothers at or near term, offered opportunity for study of this exchange. The titer of both complement-fixation and agglutination-inhibition antibodies in mother and infant were measured.

In the first case mumps developed in a mother two weeks before delivery of a normal infant. The titers in the latter were of the same magnitude as the mother's and showed no decrease in a three-week period of observation. The second case had its clinical onset on the day of delivery and the baby showed no significant titer of antibodies at this time although the mother had significant titer of both antibodies. The appearance of antibodies in the baby was not detected. Breast milk from the mother showed neither antibody nor was virus isolated. The third case developed eighteen days before the birth of a normal infant who showed a steady decrease in titer over an eighty-five-day period of observation. The fourth case occurred thirty-eight days after birth. The infant showed significant antibody fifteen days after the onset of the mother's disease although no clinical disease was noted. Breast milk showed no antibody nor was virus isolated.

A series of twenty-six mothers and their infants was studied, comparing the titer of these antibodies in the mother's blood with the titer in the placental blood. There was no significant difference found in the magnitude of titer of these antibodies.

COMBINED ACTION OF PENICILLIN WITH STREPTOMYCIN OR CHLOROMYCETIN ON ENTEROCOCCI IN VITRO. *E. Jawetz, M.D., J. B. Gunnison, M.D. (by invitation) and V. R. Coleman, M.D. (by invitation). San Francisco, Calif.* (From the Divisions of Bacteriology, Medicine and Pediatrics, University of California Medical School.)

Synergistic effects of low magnitude have recently been demonstrated *in vitro* with a number of antibiotics. Simultaneous therapy with penicillin and streptomycin has resulted in striking cures of bacterial endocarditis due to enterococci. The possible mechanism of this apparent synergism was studied *in vitro*. It was found that penicillin alone, tested in a wide range of concentrations, was bactericidal for viridans streptococci but mainly bacteriostatic for enterococci, killing only part of the bacterial population. Streptomycin-penicillin mixtures on the other hand promptly and uniformly destroyed all enterococci. Organisms surviving after exposure to penicillin alone were neither more resistant to penicillin nor more susceptible to streptomycin than the remainder of the strain population. The combined antibiotic effect was consequently not due to action of one agent on organisms resistant to another.

Streptomycin-penicillin mixtures resulted in a greatly increased rate of bactericidal action beyond the optimal rate obtainable with any concentration of penicillin alone. The addition of 25 or 50 micrograms/ml. of streptomycin to 6 to 30 micrograms/ml. of penicillin resulted in a ten- to several hundred-fold enhancement of penicillin activity on enterococci. Of several possible mechanisms for this antibiotic synergism the evidence obtained thus far favors the importance of the great increase in bactericidal rate of streptomycin-penicillin mixtures over that of penicillin alone.

Chloromycetin (10 micrograms/ml.) alone had no significant action on enterococci *in vitro*. However, this amount of chloromycetin added to various concentrations of penicillin resulted in a great decrease of the bactericidal rate below that of penicillin alone. This apparent antagonistic action of chloromycetin was observed with nine strains of enterococci. The possible clinical implications of these findings are discussed.

THERAPY OF RAYNAUD'S DISEASE WITH BENZYL-IMIDAZOLINE. *John B. Lagen, M.D. San Francisco, Calif.* (From the University of California School of Medicine.)

Raynaud's disease is one of the few peripheral vascular disorders which is functional in etiology. The involved extremities are normal between attacks although repeated attacks eventually lead to organic changes. The sympatholytic drugs offer a new medical approach to the problem of therapy. Benzyl-imidazoline (priscoline®) has the advantage over other drugs of this type in that it may be given orally.

In the series reported only the oral preparation of priscoline® was given. No other treatment, either drug or procedure, was used. Published reports on priscoline® indicated that too high an initial dose schedule tended to produce side reactions. A method of graduated increase of dose which produced no side reactions was used in this series. This schedule prescribed a tablet of the drug twice a day for three days, then three times a day for four days, given after meals. The second week a fourth tablet was prescribed at bedtime. At the end of this time the patients were seen and a decision made as to further dosage.

In three instances in which the patients had necrotic areas on the tips of one or more fingers, a gradual increase in dosage to eight tablets daily was required to prevent further attacks and to permit healing of the involved areas. Most patients remained free of attacks on a dosage level of four to six tablets per day. After some weeks of this therapy the dosage was reduced to two or three tablets per day. In the fifteen patients treated freedom from attacks was achieved with no change in the patient's mode of life.

CARDIAC EFFECTS OF INTRAVENOUS VERATRUM VIRIDE. *Stephen R. Elek, M.D., John D. McNair, M.D. (by invitation) and George C. Griffith, M.D. Los Angeles, Calif.* (From the Department of Cardiology, University of Southern California School of Medicine.)

The studies of Fries and co-workers have stimulated interest in the blood pressure-lowering action of Veratrum viride. We have given

twenty-six intravenous injections of veratrone® (Parke, Davis and Co.) to twenty patients with established essential hypertension and hypertensive heart disease. The dose varied from 3 to 9 minims, given in from one to three injections; the dose of a single injection varied from 1 to 4 minims. The two major effects studied were lowering of the blood pressure and effect on the electrocardiogram.

All patients showed a significant drop in blood pressure, ranging from 18 to 44 mm. Hg systolic and from 14 to 80 mm. Hg diastolic. This effect occurred promptly, reaching its maximum action in from eight to nineteen minutes after the start of intravenous injection. A more significant hypotensive drop resulted from a single injection of 2 to 3 minims than from divided doses. The hypotensive fall lasted for several hours and in some patients for twenty-four hours. One of the largest decreases of blood pressure was from 240/140 to 92/62 mm. Hg; at these lowered blood pressure levels no evidence of shock appeared in any patient.

The electrocardiogram showed a consistent brachycardia. A hitherto unreported finding was the occurrence of inverted T waves, notably in Lead V_4, without any other symptomatology of myocardial ischemia; the mechanism whereby Veratrum viride causes this is suggested.

Atropine did not prevent but did quantitatively alter the hypotensive change when given before or after Veratrum viride. Similarly, the resulting bradycardia was usually not altered by atropine. Neo-synephrine®, administered intravenously to three patients after Veratrum viride, elevated the lowered blood pressure, changed the altered T waves towards normal, but did not influence the bradycardia.

Our findings indicate that veratrone® produces an intense and prompt peripheral vasodilation in hypertensive patients and, also, vagal stimulation and bradycardia, which is not prevented by atropine.

EVALUATION OF THE METABOLIC AND CLINICAL EFFECTS OF ADRENOCORTICOTROPHIC HORMONE AND OF A PEPTIDE MIXTURE DERIVED FROM PURE ADRENOCORTICOTROPHIC HORMONE. *Laurance W. Kinsell, M.D. and (by invitation): Choh Hao Li, M.D., Sheldon Margen, M.D., George D. Michaels, M.D., Marcus A. Krupp, M.D., Ephraim P. Engleman, M.D. and Robert H. Frantz, M.D. San Francisco and Oakland.* (From the Division of Medicine, University of California Medical School, the Metabolic Research Unit, University of California.)

Adrenocorticotrophic hormone administration has been shown to produce significant changes in the urinary excretion of nitrogen, phosphorus, potassium, sulfur, 17-ketosteroids and other urinary constituents. Consistent changes also have been reported in the formed elements of the blood. In addition, most impressive clinical changes have been noted in individuals with a wide variety of diseases following the administration of adrenocorticotrophin. The relationship between the metabolic changes and the clinical changes noted is by no means clear.

Whole ACTH was partially hydrolyzed with pepsin. All remaining protein material was precipitated with 10 per cent trichloracetic acid. Administration of the remaining peptide mixture in a dosage of 100 mg. daily to a human subject with rheumatoid arthritis resulted in metabolic changes which were similar to or identical with those resulting from the administration of whole ACTH to the same subject at a later date. Prompt and impressive improvement in the clinical manifestations of the arthritis occurred in response to the peptide mixture as well as to the whole ACTH.

LEUKOCYTE CHANGES FOLLOWING INTRAMUSCULAR INJECTION OF EPINEPHRINE AND EPINEPHRINE CONGENERS, WITH OBSERVATIONS ON THE ALTERATIONS INDUCED BY ADRENERGIC BLOCKING AGENTS. *A. J. Samuels, M.D. (by invitation), H. H. Hecht, M.D., Frank Tyler, M.D. (by invitation) and Robert Carlisle (by invitation). Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

The influence of epinephrine on total leukocyte count, neutrophils, lymphocytes and absolute number of eosinophils in the peripheral blood was investigated in twenty subjects from the inception of the response to six hours following the injection. Counts were usually taken at five- to ten-minute intervals. In certain subjects the results were correlated with the effects of epinephrine and epinephrine congeners on blood sugar levels, heart rate and electrocardiogram, oxygen consumption, peripheral

pressures, total peripheral resistance and blood flow as estimated by catheterization studies.

Epinephrine was administered in doses up to 1 mg. L-nor-epinephrine (arterenol®-Merck) was used as a representative agent causing peripheral vasoconstriction without cardiac stimulation (four patients), isuprel as an example of a peripheral vasodilator substance of the epinephrine group (three patients). Epinephrine blocking agents were employed in 13 instances using an ergot alkaloid (DHO-180-Sandoz), an imidazole derivative (C-7337-Ciba) and a dibenzyl-nitrogen mustard (dibenamine®-Smith, Kline & French).

Epinephrine and nor-epinephrine (somewhat less intense) caused a significant primary response with increase in neutrophiles (53 per cent), lymphocytes (165 per cent) and eosinophiles (89 per cent) with a maximum effect at fifteen minutes after the injection and returning to normal within one hour. Isuprel failed to elicit a predictable response. C-7337 alone caused a slight decrease in all cellular components during the first hour and partially suppressed the primary response to epinephrine. DHO-180 did not alter epinephrine leukocyte response and dibenamine® gave equivocal results. A previously adequate neutrophile response following administration of epinephrine was blocked in a few patients subjected to splenectomy. The primary neutrophile rise appears influenced by the absence of the spleen. The response of cellular elements otherwise was presumably independent of blood glucose, peripheral blood flow and the peripheral resistance.

The secondary change commenced imperceptibly at the end of the first hour, reaching a maximum response within two to four hours and was characterized by a rise in total number of white cells (55 per cent) and neutrophiles (98 per cent) and a fall in lymphocytes (18 per cent) and eosinophiles (48 per cent). The results with epinephrine and L-nor-epinephrine were similar except that the latter compound failed to cause a fall in eosinophiles. Adrenergic blocking agents were incapable of altering secondary response.

Although the detailed mechanism of the changes needs further elucidation, the primary response appears to be concerned with complex circulatory adjustments, the secondary response with stimulation of the hypothalamic-pituitary-adrenal system.

EOSINOPHILE AND URIC ACID CHANGES AFTER EPINEPHRINE AND ADRENOCORTICOTROPHIC HORMONE IN NORMAL PATIENTS AND IN ADRENAL CORTICAL INSUFFICIENCY. *Arthur A. Marlow, M.D. and Robert A. Kallsen, M.D. (by invitation). La Jolla, Calif.* (From the Scripps Metabolic Clinic.)

The effects of epinephrine and ACTH injection on the circulating eosinophiles and urinary uric acid/creatinine ratio have been investigated in patients with and without Addison's disease. The eosinophile decrease four hours after either 0.3 or 0.5 mg. of epinephrine subcutaneously was the same as after 2.5 to 25 mg. of ACTH intramuscularly and failed to decrease significantly in Addison's disease. No change was noted in the urinary uric acid/creatinine ratio following epinephrine or small doses of ACTH, but marked increases in uric acid excretion followed the larger doses of ACTH in normal individuals. This suggests that the eosinophile is more sensitive to changes in adrenal cortical activity and that epinephrine stress does not elicit a maximal adrenal cortical response. Blood cortin levels following epinephrine and ACTH will be reported.

Patients who had debility suggestive of more severe Addison's disease were prepared with desoxycorticosterone and salt prior to epinephrine or ACTH. Under these conditions epinephrine stress was well tolerated. Low cost and ready availability of epinephrine make it a useful tool in the diagnosis of Addison's disease.

EVALUATION OF 17-KETOSTEROID, ESTROGEN AND GONADOTROPHIN EXCRETION IN PATIENTS WITH SPINAL CORD INJURY. *Robert C. Rosenquist, M.D. (Introduced by John E. Peterson, M.D.) Van Nuys, Calif.* (From the Birmingham Veterans Administration Hospital.)

Thirty-two paraplegic and quadriplegic patients have been studied. 17-Ketosteroid excretion levels ranged from 7.1 to 37.9 mg. per twenty-four hours (normal 7–18 mg. per twenty-four hours for males). Eleven (34.3 per cent) of the excretion values were elevated. Estrogen excretion varied from 1.9 to 92.6 micrograms per twenty-four hours (normal 6–20 micrograms per twenty-four hours for males); twenty-seven of the thirty-two determinations (84.2 per cent) yielded excretion values above normal, while an excretion value below normal (1.9 micrograms) was found in only one case. Gonado-

trophin bioassays were performed in thirty of the thirty-two cases; twenty-six of the determinations (86.6 per cent) gave values of less than 6.6 mouse units excreted per twenty-four hours; the remaining four cases gave values varying between 6.6 and 52 mouse units excreted per twenty-four hours. Normal males of proved fertility excreted from less than 6.6 to 52 mouse units per twenty-four hours. It is of interest that paraplegics have such low gonadotrophin titers in view of the severe degree of testicular atrophy (germinal epithelium) present in these patients.

Estrogens, in the male, are secreted by the adrenal cortex and destroyed in the liver. In an attempt to discover whether the increased estrogen excretion was due to increased production in the adrenal or decreased destruction in the liver, a series of liver function tests were done. With a few minor exceptions the liver function tests were normal. In the cases with abnormal liver function tests the estrogen excretion levels were not greater than in the cases with normal function tests.

In an attempt to explain these findings it has been postulated that a state of adrenal hyperactivity exists and may be a manifestation of the adaptation syndrome described by Selye. The low gonadotrophin titers may be due to pituitary inhibition by the increased estrogens.

EFFECTS OF INTRA-ARTERIAL ADMINISTRATION OF NITROGEN MUSTARD. *Howard R. Bierman, M.D., Ralph L. Byron, Jr., M.D., Ear. R. Miller, M.D. and Michael B. Shimkin, M.D. San Francisco, Calif.* (From the Laboratory of Experimental Oncology, University of California Medical School.)

The lesions of some cutaneous neoplasms (mycosis fungoides, metastatic renal adenocarcinoma, mixed tumor of the parotid) have been shown to fluoresce selectively immediately after injection of fluorescein or riboflavin into the artery supplying the region of the tumor. A technic for catheterization of the aorta, coeliac axis, superior mesenteric and renal arteries has been developed. This permits injection of therapeutic agents such as nitrogen mustard and radioactive substances more directly to areas of neoplastic involvement. Twenty administrations of nitrogen mustard into arteries leading to various neoplasms have been studied. Greater therapeutic efficacy than with the same dosage given intravenously has been shown in mycosis fungoides. There is less depressant effect on the hematopoietic system with intra-arterial than with intravenous administration of nitrogen mustard, thus permitting larger doses to be used. The effect of intra-arterial administration of larger doses of nitrogen mustard (above 0.6 mg./kg. body weight) on other lymphomas and metastatic radioinsensitive tumors is being evaluated.

PLASMA CHOLESTEROL IN RATS FOLLOWING LIGATION OF THE BILE DUCT AND INTRAVENOUS INJECTION OF FREE CHOLESTEROL. *Sanford O. Byers, Ph.D. (by invitation) and Meyer Friedman, M.D. San Francisco, Calif.* (From the Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research.)

The mechanism responsible for the rise in free cholesterol content of blood plasma following biliary obstruction is not clear. Likewise, opinion is not uniform concerning the changes in blood content of esterified cholesterol after biliary obstruction. It therefore was believed that further information concerning these two questions might be obtained if animals with ligated bile ducts were subjected acutely to additional cholesterol load. The latter was accomplished by the intravenous injection of a specially prepared suspension of free cholesterol stabilized with sodium laurate.

The bile ducts of fifty rats were ligated after preoperative blood samples had been obtained. The average free cholesterol content of their plasma before ligation was 28 mg. per 100 cc. Twenty-four and seventy-two hours after duct ligation the free cholesterol content was 81 and 215 mg. per 100 cc. No change occurred in the cholesterol ester content of plasma after ligation. Twenty-three rats were subjected to ligation of the bile duct after which they received a single injection of free cholesterol (20 mg. of cholesterol per 100 gm. of body weight). The free cholesterol content of their plasma twenty-four and seventy-two hours after ligation was 152 and 280 mg. per 100 cc., respectively. A comparison of these latter values with those found in the rats which had not received intravenous cholesterol indicates that regardless of the interval after ligation, the difference in the free cholesterol contents of the two series remained approximately the same, namely, 65 to 71 mg. per 100 cc. This indicated that the rate of entrance of free cholesterol into the plasma, possibly the rate of production, is

constant and independent of its plasma concentration. However, the cholesterol ester content of the ligated rats which had received intravenous cholesterol was unchanged twenty-four hours after ligation.

These results indicate that a rapid and large increase in the free cholesterol component of rat blood plasma occurs after ligation of the biliary duct without a quantitatively comparable rise in esterified cholesterol. Furthermore, the results suggest that the regulation of the free cholesterol content of plasma is not determined primarily at its source of entrance into the blood but rather at the site of its elimination or destruction, the hepatobiliary system.

RELATIONSHIP OF RENIN TO ACUTE PHASE OF RENAL HYPERTENSION IN THE RABBIT: TACHYPHYLAXIS. *Jack Flasher, M.D. (by invitation) and Douglas R. Drury, M.D. Los Angeles, Calif.* (From the University of Southern California.)

Many investigators have shown that repeated injections of renin at short intervals result in reduction and finally absence of the pressor response. It seems unlikely that a substance that exhibits this tachyphylaxis phenomenon could be the humoral agent in experimental renal hypertension. Further, if one were to consider an animal with renal hypertension (during the phase when the pressor substance was still present in the blood), one would expect the blood pressure to return to normal when it was made tachyphylactic to injected renin. We performed such an experiment in rabbits with renal hypertension of up to five to fifty-five days' duration and found that the blood pressure remained close to (slightly above) the initial hypertensive level when they were made tachyphylactic to hog renin; these rabbits were tachyphylactic to injected rabbit renin. Normal rabbits also exhibited this slight elevation of blood pressure when they were made tachyphylactic. The dose of renin and the interval that was used in this experiment was such that we obtained absolute tachyphylaxis; i.e., the same doses and doses up to ten times as large did not produce a pressor response. We have also produced tachyphylaxis with smaller doses of renin. In the latter the tachyphylaxis is only relative; although the animal no longer reacted to that dose of renin, some pressor response to a larger dose was obtained.

There is some evidence that tachyphylaxis to renin may merely represent the depletion of substrate (hypertensinogen). We intend to investigate this since it bears on the interpretation of the aforementioned experiments.

URINARY EXCRETION OF DIGITOXIN IN MAN. *Meyer Friedman, M.D., Rene Bine, Jr., M.D. (by invitation) and Sanford O. Byers, Ph.D. (by invitation). San Francisco, Calif.* (From the Mount Zion Hospital, The Harold Brunn Institute for Cardiovascular Research.)

By means of the embryonic duck heart preparation and a microchemical method of extracting minute quantities of digitoxin from large volumes of urine it has been found possible for the first time to determine the urinary excretion of digitoxin in subjects receiving the drug. The urinary excretion of digitoxin for twenty-four hours was determined in six normal men and in seven normal women after 1.2 mg. of the drug was ingested (in a period of six hours). The rate of excretion for twenty-four hours was studied again in four of the six men. Also, the excretion rate after the first twenty-four hours was studied in five of these men and in five of the women.

It was found that an average of 59 micrograms of digitoxin was excreted by men during the first twenty-four hours after ingestion of the aforementioned dose. The average daily excretion rate two, three, six, nine and twelve days after ingestion was 49, 41, 25, 18 and 10 micrograms, respectively. One of the five males ceased to excrete a detectable amount (i.e., less than 5 micrograms) of digitoxin twelve days after initial ingestion of the drug; one of the remaining four males ceased excreting the drug fifteen days after ingestion and only one of the subjects continued to excrete detectable digitoxin after the eighteenth day postingestion (by the twenty-seventh day postingestion). Approximately a maximum of 41 per cent of the orally given dose of 1.2 mg. of digitoxin was excreted in the urine of these five subjects.

The female subjects apparently excrete considerably more digitoxin during the first three days after oral ingestion of 1.2 mg. Thus, an average of 82 micrograms of the drug was found in the first twenty-four-hour urine output of the seven women. The average excretion rate of women on the second and third days after ingestion (70 and 53 micrograms, respectively) also was greater than that of the men. Four of the subjects were studied beyond the third day postingestion. It was found that the average daily excretion rate six, nine, twelve and fifteen

days was 23, 37, 18 and 22 micrograms, respectively. Again, in contrast to the males, three of the four females continued to excrete digitoxin on the eighteenth day postingestion; two continued on the twenty-first day but none excreted detectable amounts of digitoxin on the twenty-fourth day after ingestion. A maximum of approximately 46 per cent of the given dose was excreted in the urine of these patients.

These results indicate that a significant amount of digitoxin (41 to 46 per cent of administered dose) is excreted (over a period of fifteen to twenty-four days) in the urine of normal subjects who have received a single digitalizing dose of digitoxin (1.2 mg.). Females appear to excrete larger quantities over a longer period.

INFLUENCE OF INFLAMMATION, COBALT ADMINISTRATION, DIET AND PYRIDOXINE DEFICIENCY ON IRON ABSORPTION. *Clark J. Gubler, Ph.D. (by invitation), G. E. Cartwright, M.D. and M. M. Wintrobe, M.D. Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

Iron absorption was studied in rats in the presence of inflammation (bacteria, turpentine), cobalt administration and pyridoxine deficiency. Constant amounts of iron were fed and the total iron absorption was determined by ashing the animals. A total of 166 rats, divided into "control" and "infection" groups, were given equal amounts of either radioactive or non-radioactive iron orally or by stomach tube.

In all instances the infected rats retained less iron than did the corresponding controls. Rats with sterile turpentine abscesses likewise retained less iron than corresponding control rats. However, rats treated with turpentine and cobalt absorbed as much or more iron than did the controls. Rats receiving cobalt alone absorbed somewhat more than did control rats but the difference was not significant.

Thirty rats received a dog chow diet *ad libitum*. Their iron retention as compared to that of rats on a purified diet with supplemented inorganic iron was only about half as great in spite of the fact that their iron intake was 3.5 times as great.

The iron retention following an equal intake of iron was compared in control and in pyridoxine-deficient rats. The pyridoxine-deficient rats retained significantly greater quantities of iron than did the control rats.

It appears from these observations that inflammation is associated with a decrease in the absorption of iron from the gut in rats. The administration of cobalt does not significantly increase absorption above the control value but it appears to counteract the inhibiting effect of inflammation on iron absorption. It also appears that diets high in phosphates markedly inhibit iron absorption and that pyridoxine deficiency is associated with an increased retention of iron.

THE PERSON WITH ESSENTIAL HYPERTENSION: (DYNAMIC PSYCHOLOGICAL FACTORS IN THE DISEASE). *Samuel P. Hunt, M.D. (by invitation) and Maurice Sokolow, M.D. San Francisco, Calif.* (From the Divisions of Psychiatry, University of California Medical School.)

Many internists seem to concur with Goldring's statement that "Psychotherapy is the most valuable single device in the rehabilitation of the hypertensive patient." To study further the hypertensive personality and to attempt to define its relation to the disease thirty unselected younger patients with proved hypertension of varying degrees of severity were examined psychiatrically. Special attention was directed to the childhood situation, to the prehypertensive personality, to time relations between periods of emotional stress and appearance of symptoms, to the nature of the symptoms and to emotional states concomitant with the development of the disease.

Evidence was accumulated suggesting the following: (1) The early symptoms, e.g., headache, dizziness, fatigue, are indications of neurotic conflict the nature of which can be determined by the use of psychiatric technics: (2) Patients with hypertension suffer from disturbances in their inter-personal relationships not readily apparent to the untrained observer. The main features of these are excessive fear of latent hostility, sexual inhibition, obsessive-compulsive character traits, depressive trends and a morbid unconscious dependence. (3) Some evidence was obtained to indicate that grateful and dependent attitudes bound to the physician may be responsible at times for symptomatic improvement under diverse treatments. (4) In all cases studied the discovery of the hypertension was preceded in the recent years by increasing stress and tension connected with such inter-personal factors as attitudes in mar-

riage, toward the employer and toward the death of an emotionally significant person.

The conclusions were reached that emotional factors are important in hypertensive cardiovasculorenal disease and may influence its course.

RESTORATION OF LOW BLOOD SODIUM AND CHLORIDE LEVELS WITH ISOTONIC AND HYPOTONIC SOLUTIONS BY VEIN. *Wm. W. Hurst, M.D. (by invitation) and Ferdinand R. Schemm, M.D. Great Falls, Mont.* (From the Dept. of Medicine, Great Falls Clinic and Western Foundation for Clinical Research.)

In our experience with the restoration of low blood sodium and chloride levels the best clinical results have been obtained by providing required amounts of electrolyte with proportionately larger amounts of water. We have not been able to obtain evidence that a low serum sodium alone indicates a state of dilution of the extracellular fluid. Our data suggest that low levels of sodium and/or chloride usually exist with an actual concentration of the extracellular fluid as well as with a loss in total volume of the extracellular fluid.

Water and electrolyte balance data from two patients are reported. When treatment was started both were comatose, markedly oliguric and azotemic. In the first instance, in a three and one-half day period, 20.5 L. of intravenous fluids were given containing 803 mEq. of sodium and 1,264 of chloride, representing the equivalent of about 8 L. of isotonic electrolyte plus 12.5 L. of plain water. In the second instance, in a three and one-half day period, 24 L., were given containing 873.5 mEq. of sodium and 1,179.5 of chloride, representing the equivalent of 8 L. of isotonic electrolyte plus 16 L. of plain water. In both instances the sodium containing solutions as given were one-half isotonic strength except for 3 L. which were isotonic.

In these two periods, respectively, the plasma sodiums rose from 122 and 120, to 135 and 144 mEq./L.; the plasma chlorides from 50.5 and 48 to 90 and 86 mEq./L. the carbon dioxide combining power fell from 104 and 77 to 82 and 65 volumes per cent; the blood urea nitrogen fell from 130 and 100 to 36 and 14 mg. per cent; and the serum specific gravity fell from 1.0280 and 1.0297 to 1.0233 and 1.0214. The lower specific gravities appeared optimal and were maintained during convalescence. In both a large positive balance of sodium was maintained by the kidneys in spite of the high water intake by vein and a urine water output of from 3,000 to 5,000 cc. daily.

CHANGES IN PULSE VELOCITY DURING INCREASED INTRATHORACIC PRESSURE. *Chester Hyman, Ph.D. (by invitation) and Douglas R. Drury, M.D. Los Angeles, Calif.* (From the University of Southern California.)

As part of a study on reflexly induced changes in the peripheral arteries, a series of measurements were made of the pulse velocity during increased intrathoracic pressure. Determinations were made on a small group of healthy young men, using a modified oscillometric technic to pick up the pulse from the arteries under consideration. Both the brachial artery (from the axilla to the wrist) and the femoral artery (from the groin to the ankle) were investigated. The output from the oscillometers was taken to a high speed recording oscillograph and measurements were made on a number of pulse transits for each determination. In this way random variations were minimized.

In all cases there was a significant increase in the velocity of the pulse wave transmission. This increase ranged from 20 to 30 per cent of the control value and was outside any possible chance. The control values in the subjects studied varied from 6.4 to about 11.0 meters per second, while the values recorded during the periods of increased intrathoracic pressure (induced by either a Valsalva maneuver or by a modified Flack test) ranged from 8.7 to 20 meters per second.

The increased pulse velocity was noted in the first beat after the increase in intrathoracic pressure was applied and continued through to the end of the period, usually about thirty seconds.

These findings, lacking simultaneous measurements of intra-arterial pressure, cannot be taken as conclusive evidence but are at least suggestive of a marked diminution in arterial caliber which, in turn, suggests an active constriction of the artery as a consequence of increased intrathoracic pressure.

METHOD FOR THE DETERMINATION OF THE COPPER CONTENT OF PLASMA, WHOLE BLOOD, ERYTHROCYTES AND LEUKOCYTES. *M. E. Lahey, M.D. and Clark J. Gubler, Ph.D. Salt Lake City, Utah. (Introduced by M. M. Wintrobe, M.D.)* (From the De-

partment of Medicine, University of Utah College of Medicine.)

When it was decided to undertake a thorough study of copper metabolism and its relationship to hematopoiesis, it became apparent that a simplified method for the determination of copper in blood and its components is needed. Methods in current use require either ashing of the material prior to colorimetry, repeated extractions of the material with trichloracetic acid or extraction of the color complex with amyl alcohol; each method has certain objectionable features.

A simple and accurate method for the determination of copper in small samples of plasma, whole blood, red blood cells and white blood cells is outlined. The proposed method is based on the principle used for the determination of serum iron, namely, the liberation of copper from its protein binding by the use of dilute HCl, followed by removal of the proteins with trichloracetic acid. This leaves the copper in the supernatant in such a form that it can be measured directly by the use of sodium diethyldithiocarbamate as color reagent. The method can be adapted to large or small volumes of material. With a Beckman spectrophotometer or similar instrument, determinations can be made on as little as 1.0 ml. of plasma, blood or cells, with an accuracy as great as reported for other procedures. Recovery of added copper ranged from 97 to 110 per cent. The procedure requires only forty to fifty minutes for completion.

Various applications of this method to the study of copper metabolism will be discussed.

CARDIAC EFFECTS OF DIHYDROERGOCORNINE. *D. W. Leik, M.D. (by invitation) and Stephen R. Elek, M.D. Los Angeles, Calif.* (From the Department of Cardiology University of Southern California School of Medicine.)

Wendkos' studies in inverted T waves in patients with cardiac and general anxiety states have indicated that this finding is due to excessive sympathetic stimulation (tone) of the heart. We were interested in studying the participation of the sympathetic nervous system in inverted T waves resulting from myocardial infarction by testing with the sympatholytic agent DHO-180. Five males in the third to fifth week convalescence from myocardial infarction and three with established angina who had inverted T waves were studied. In addition, two patients with auricular fibrillation, one with supraventricular tachycardia and two with clinical hyperthyroidism, one of whom had electrocardiographic abnormalities due to hyperthyroidism, were tested.

DHO-180 was given intravenously in doses of 0.5 to 1 mg. to fourteen patients resulting in a slight to moderate decrease in systolic and diastolic blood pressure and heart rate. One patient with hypertension and tachycardia showed the most marked lowering of both blood pressure and pulse.

Only one of the five patients with myocardial infarction showed return of the inverted T waves in the chest leads toward normal. In one of the three patients with angina the inverted T waves became upright in two leads. In one patient with supraventricular tachycardia normal sinus rhythm occurred thirty minutes after injection. The auricular fibrillation in two patients was unchanged. In two young hyperthyroid patients DHO-180 produced an increase in amplitude of T waves in two leads in one, while in the more severe case control inverted T waves became upright. In the latter patient a more marked sympathetic activity is assumed to be the cause of the electrocardiographic abnormalities.

Our observations indicate that the sympathetic nervous system probably does not participate in the inversion of T waves due to organic cardiac disease but does influence the T wave abnormalities found in hyperthyroidism.

PROTEINURIA EFFECT ON TOXICITY OF MERCURIAL DIURETICS IN THE RAT. *Richard W. Lippman, M.D. Los Angeles, Calif.* (From the Institute for Medical Research, Cedars of Lebanon Hospital.)

Rats were administered an intravenous dose of mercurial diuretic (mersalyl or meralluride sodium) varying from 0.26 to 1.95 mg Hg. The control animals received intraperitoneal injections of 0.85 per cent sodium chloride solution. At autopsy the kidneys of the control animals showed severe, acute, necrotizing nephrosis. The severity, and evidence of healing, was related to the dose and time interval until kill. Some of the animals died before the experiment was terminated at the end of one week.

The experimental animals received intraperitoneal injections of bovine albumin in the dosage used by Addis to produce massive proteinuria. These animals receiving the mercurial after the onset of proteinuria were unaffected in

the gross. Microscopic sections of the kidney revealed slight degrees of acute nephrosis. This effect was attributed to the inhibition of mercurial reabsorption when the tubules are saturated with protein.

The experimental animals which received the mercurial before the onset of proteinuria were most severely affected. Most of the animals died before termination of the experiment at one week and the kidneys were subject to the most severe tubular destruction of acute, necrotizing nephrosis. This effect was attributed to the more rapid reabsorption of mercurial, concomitant with more rapid reabsorption of protein during the tubular loading phase.

LONG-TERM STUDY OF THE HYPOTENSIVE EFFECTS OF VERATRUM VIRIDE IN HYPERTENSIVE PATIENTS. *J. D. McNair, M.D. (by invitation) and George C. Griffith, M.D. Los Angeles, Calif.* (From the Department of Cardiology, University of Southern California School of Medicine.)

This study was carried out to determine if Veratrum viride is an effective agent for lowering blood pressure in a group of essential hypertensive patients. The drug used was vertavis, which is Veratrum viride (Irwin Neisler and Co.), standardized in craw units with 10 craw units to each tablet. The tablets used for placebo were made by the same company and were in every way similar to the tablets containing the drug.

All of the patients were regular visitors to various clinics at this hospital and, therefore, have been carefully studied to determine the type of hypertension. The patients were unselected and originally comprised a group of twenty-eight essential hypertensives; however, one patient was dropped because the blood pressure was too low and five patients stopped attending the clinic before treatment was begun. The remaining twenty-two patients who comprised this study all had blood pressures above 175 mm. Hg systolic and 100 mm. Hg diastolic. The average age for the group was fifty-three years, the youngest being thirty-two and the oldest eighty-six. There were fourteen females and eight males, twelve white and ten Negro patients. The average duration of hypertension was nine years, the shortest six months and the longest thirty years. The period of study for each patient varied between two and five months.

Fifty per cent of the patients claimed they were improved symptomatically, but there was no correlation between change in blood pressure and symptomatic improvement. The average change in blood pressure while taking the drug was a drop of 7 mm. systolic and a drop of 6.6 diastolic pressure. The average pulse drop was 3 beats per minute. However, the normal variation of the blood pressure in the patient without treatment was far greater than the average change in blood pressure under treatment.

Veratrum viride, given in the form of vertavis® by mouth, had no significant effect on the blood pressure of twenty-two unselected hypertensive patients despite the fact that the drug was given to the point of tolerance in each patient.

RESONANT PHENOMENA OF THE AORTA AND SMALLER ARTERIES. *John P. Meehan, M.D. (Introduced by Dr. Douglas R. Drury). Los Angeles Calif.* (From the University of Southern California.)

The study of some of the resonant phenomena of the aorta has been approached by a direct experimental method. Free pressure oscillations were produced experimentally in the aorta of an intact animal. These oscillations were introduced into the aorta through a sound inserted in the left carotid artery and extending to the base of the aorta. Simultaneous pressure records were made from the base of the aorta, the femoral and the brachial arteries when feasible. The magnitude, frequency and velocity of transmission of the free oscillations to the smaller arteries were determined from the records. The experiments were performed on animals with normal arterial pressures as well as on animals made hypotensive by bleeding and hypertensive by the intravenous administration of adrenalin solutions.

The frequency of the experimentally produced free pressure oscillations proved to be the same as those usually seen in the aorta following closure of the aortic valve. The frequency was only slightly increased in hypertensive animals and very much reduced in hypotensive animals. The transmission to the smaller arteries was variable but usually better to the brachial artery. In markedly hypotensive animals the oscillations were not transmitted to the smaller arteries. The experiments were carried out on large rabbits, cats, dogs and small goats in an effort to determine if there were any fundamental differences in the various animals frequently used as experimental subjects. Only slight variations in the data were noted and

these were apparently best correlated with the size of the animal.

RESULTS OF TREATMENT IN CORONARY ARTERIOSCLEROSIS WITH LIPOTROPIC AGENTS. *Lester M. Morrison, M.D. and (by invitation) William F. Gonzales, M.D. Los Angeles, Calif.* (From Los Angeles County General Hospital and Department of Internal Medicine, College of Medical Evangelists.)

Clinical experiences are reported with the use of various lipotropic agents such as choline, methionine and inositol in the treatment of coronary arteriosclerosis. In one group a series of 115 patients with proved coronary thrombosis and myocardial infarction were treated with choline after recovery from the acute attack and discharge from the hospital. These patients were divided into three groups: (1) fifty-two patients given choline for one year, (2) a group of thirty-five given choline for two years and (3) a group of twenty-eight patients given choline for three years.

The dosage of choline varied from 6 to 32 gm. daily. These series of patients were compared with a group of "alternate controls" consisting of 115 patients with proved coronary thrombosis and myocardial infarction who were discharged from the hospital under identical conditions. The patients in this series were observed over the same period of time and did not receive choline.

Detailed analyses of each choline-treated group as compared with its "control" series revealed that the subsequent mortality rate of patients was significantly reduced under choline treatment.

One mode of action of choline in the treatment described is demonstrated through its effect in increasing the phospholipid turnover by the liver, and increasing the serum lipid phosphorus levels in these patients. In this way the phospholipids maintain the serum lipids in finer dispersion and suspension and increase the stability of the serum lipo-protein complexes and the colloidal plasmatic stability. It is suggested from this evidence, as well as from that previously presented, that in this way the further development of arteriosclerosis is arrested.

These studies suggest that the lipotropic agent, choline, is of value in the treatment of coronary arteriosclerosis and merits further trial and observation in this disease.

ANALGESIC EFFECTS OF NITROUS OXIDE AND MEPERIDINE, ALONE AND COMBINED WITH AMPHETAMINE. *Mark Nickerson, Ph.D., Salt Lake City, Utah.* (From the Department of Pharmacology, University of Utah College of Medicine.)

Potentiation of morphine analgesia by amphetamine suggested a study of the effect of this central nervous system stimulant on the analgesia produced by other agents. Experiments were carried out on groups of eight to ten medical students. Pain thresholds were determined by two methods: (1) the time required for deep pain to develop in a hand placed in water at 4°C. after prior equilibration at 30°C. and (2) the Hardy-Wolff-Goodell radiant heat technic for cutaneous pain. Control thresholds and their normal variation without medication were first determined. Meperidine (100 mg. orally) or N_2O (33 per cent in O_2 by face mask) was then administered with or without amphetamine (20 mg. orally) or dextro-amphetamine (10 mg. orally). Pain thresholds were redetermined at half-hour intervals after the administration of meperidine or after equilibration to N_2O for fifteen minutes.

Both meperidine and N_2O produced a statistically significant analgesic response. However, their relative effectiveness cannot be adequately evaluated from these data as different groups of students were involved in experiments with the two agents. Both caused a greater percentage increase in the threshold for deep pain than in that for superficial pain. The difference was considerably greater with N_2O than with meperidine and is believed to be related to the greater subjective factor in the interpretation of deep pain. Concomitant administration of amphetamine caused a significant increase in the analgesic action of meperidine, particularly when measured by the response to deep pain, but largely eliminated that of N_2O.

It is concluded that the site or mechanism of action of meperidine in producing analgesia is different from that of N_2O, that the action of N_2O is largely dependent upon a depression of higher levels of the central nervous system and that the N_2O action can be effectively antagonized by amphetamine.

EXPERIMENTAL PRODUCTION OF A NUTRITIONAL MACROCYTIC ANEMIA IN SWINE. *Jeffress G. Palmer, M.D. (by invitation),*

George E. Cartwright, M.D. and M. M. Wintrobe, M.D. Salt Lake City, Utah. (From the Department of Medicine, College of Medicine, University of Utah.)

A deficiency of pteroylglutamic acid has been produced in a total of fifty swine fed a basal diet supplemented with sulfasuxidine, a folic acid antagonist (crude methyl folic acid) and seven synthetic B vitamins. The deficiency syndrome is characterized by a macrocytic anemia, leukopenia, slight thrombocytopenia, bone marrow hyperplasia with the presence of cells resembling but not identical with the megaloblasts of pernicious anemia, a low free erythrocyte protoporphyrin content, normal serum copper and an elevated serum iron level. The blood and bone marrow return rapidly to normal following the administration of pteroylglutamic acid, pteroyldiglutamic acid, pteroyltriglutamic acid and pteroylheptaglutamic acid. Purified liver extract, vitamin B_{12}, ascorbic acid, crude desoxyribonucleic acid, crude ribonucleic acid, proteolyzed liver and marmite are only partially effective. The administration of thymine and B_{12} together does not substitute for pteroylglutamic acid.

Since 2,6-diaminopurine has been demonstrated to be a purine as well as a pteroylglutamic acid antagonist in the metabolism of certain bacteria, this compound was administered to ten pigs to see if changes in the blood and bone marrow similar to those seen in pteroylglutamic acid deficiency could be produced. The hematologic manifestations observed were a normocytic anemia and a hypoplastic bone marrow. Cells resembling megaloblasts were not observed. It appears that the metabolic abnormality produced by 2,6-diaminopurine differs from that produced by the "crude" methyl folic acid antagonist.

Attempts have been made to produce a deficiency of vitamin B_{12} in swine by raising two to five day old pigs on soybean protein rather than on a casein diet. Pteroylglutamic acid, sulfasuxidine and, in certain instances, desiccated thyroid were included in the diet. Following the administration of crystalline vitamin B_{12} to such animals a growth response was observed. The deficiency syndrome, however, was not accompanied by significant anemia or striking alterations in the bone marrow.

COMPARATIVE STUDY OF STOOL PIGMENTS IN MUSCULAR DYSTROPHY AND NORMALS. *Gerald T. Perkoff, M.D. and Frank H. Tyler, M.D.* (*Introduced by M. M. Wintrobe, M.D.*) *Salt Lake City, Utah.* (From the Department of Medicine, University of Utah College of Medicine.)

In 1939 Meldolesi et al. reported the occurrence of an abnormal pigment in the stools of patients with active muscular dystrophy and other myopathies. This pigment was reported as showing a green fluorescence in ordinary light without the addition of zinc salts and had a maximum absorption at 260–300 $\mu\mu$. It had all the characteristics of mesobilifucsin. He named this pigment "myobilin" and stated that it was not present in normal stools. Subsequently, Steffanute, using a crude dilution technic, reported markedly increased amounts of "myobilin" in stools from dystrophic patients as compared to stools from normals.

Stools from normal and dystrophic patients were analyzed for their total urobilinogen content and for the presence of "myobilin." The total urobilinogen in stools from dystrophic patients was normal. A substance having the characteristics described by Meldolesi was obtained by chromatographic separation. The pigment was found, however, in all normal stools tested as well as in stools from dystrophic patients. Measurement of the amount of pigment in the stools of normal and dystrophic patients by the dilution technic used by Steffanute showed that normal stools contained amounts of pigment equal to and in some instances greater than the amounts found in stools of dystrophic patients.

It is concluded that "myobilin" as described by Meldolesi is present in stools of normal as well as dystrophic patients and that no diagnostic or physiologic significance can be attached to this finding in muscular dystrophy. The term "myobilin" should be discarded since there is no evidence that this pigment, which is presumably mesobilifucsin, has any special relation to myoglobin or that it is related to the fundamental anomaly in progressive muscular dystrophy.

BLOOD HISTAMINE IN LEUKEMIA. *Michael B. Shimkin, M.D. and Howard R. Bierman, M.D. San Francisco, Calif.* (From the Laboratory of Experimental Oncology, University of California Medical School.)

Blood histamine in chronic myelocytic leukemia is raised to very high levels, up to 2300 micrograms per 100 cc., in comparison with

normal blood histamine of 2 to 8.5 micrograms. There is a rough parallel between the white blood cell count and the level of blood histamine in patients who are in relatively good balance with their disease. The blood histamine drops in parallel with the white blood count and basal metabolic rate in patients responding well to therapy.

In acute myelocytic leukemia, or acute exacerbations of chronic myelocytic leukemia, the blood histamine values are depressed, sometimes to less than 10 micrograms and independently of the white blood count. This finding has a very poor prognostic indication.

In chronic myelocytic leukemia injection of epinephrine produces a rise in blood histamine. In acute phases of the disease epinephrine produces a fall in histamine, suggesting a disturbance in a homeostatic mechanism, perhaps between epinephrine and histamine.

AVERAGE VOLUME OF LEUKEMIC LEUKOCYTES. PRELIMINARY REPORT. *Harold Tivey, A.B., Jonah G. Li, M.D. and Edwin E. Osgood, M.D.* (*Introduced by N. A. David, M.D.*) *Portland Ore.* (From the Division of Experimental Medicine, University of Oregon Medical School.)

Leukocytes were separated from the whole blood of leukemic patients by the panerythrocyte agglutination method of Li and Osgood. The suspension of the separated leukocytes in their own plasma was centrifuged to a constant volume in recalibrated Osgood- or Wintrobe-type hematocrit tubes and the average volume per leukocyte calculated from the leukocyte count of the plasma suspension, the suspension volume and the packed cell volume, correcting for the volume of entrapped erythrocytes.

Preliminary data indicate an average apparent lymphocytic volume (eighteen patients) of approximately 250 μ^3, apparent granulocytic volume (fourteen patients) 520 μ^3, with an average monocytic volume (four patients) of 490 μ^3. Distributions of the values contributing to these averages given are as yet too irregular to permit evaluation of standard deviations.

Case Reports

Primary Hemangio-endothelial Sarcoma of the Heart*

CAPT. FRANK J. GLASSY, M.C.† *and* FRANKLIN C. MASSEY, M.D.‡

TUMORS of the heart, both primary and secondary, are infrequent enough to warrant detailed reports of single cases; and primary, malignant cardiac neoplasms are rarer still, in a proportion to metastatic tumors of 1:16. As pointed out by Straus and Merliss,[1] "Individual experience varies considerably, since some whose experience includes as many as 30,000 autopsies have seen none, whereas others have reported three cases of primary cardiac tumor among 12,000 autopsies. When the eight cases of cardiac tumor reported from 1938 to 1942 in this country are viewed against the background of the national autopsy experience of 480,331 cases during the same five-year period reported by the American Medical Association, the incidence of primary tumor of the heart is 0.0017%, assuming all cases to have been reported." Many writers believe this percentage to be the closest to the actual incidence of primary cardiac tumors. At Madigan General Hospital this is the first primary cardiac neoplasm in 307 autopsies between 1945 to April, 1948, inclusive.

Mahaim's meticulous amassing of data on pericardial and cardiac tumors published in French in 1945 listed 329 tumors of the heart and 84 of the pericardium as having been reported in the world literature. In a footnote to his bibliography he explains, "La bibliographie americaine, bloquee par la guerre, est incomplete depuis 1942." Remarkably enough only three reports in the American literature were omitted by Mahaim. One of these was a benign tumor of the left ventricular wall successfully removed surgically by Beck[25]; the second was a fibromyxosarcoma reported by Ravid and Sachs;[24] and the third was a primary tumor of the left auricle described by B. Friedman et al.[27] Mahaim did not mention the Brazilian report of a hemangioreticuloendothelioma by Motta in 1941.[23] Leach[4] since Mahaim's published information gathered nine additional cases of primary cardiac tumor[1,2,5–7] from the literature and added two of his own, one benign and one malignant. He failed to include Burnett and Davidson's[21] single case of primary myxoma reported in 1945. W. Brown[28] described a myxoma of the heart in 1946, while Young and Hunter[22] added another myxoma to the list in 1947 and Shelburne[26] reported a case of fibrosarcoma in 1948. This would bring the total of primary cardiac neoplasms to 348. This total is exclusive of primary tumors of the pericardium.

Many authors have failed to emphasize the difference between the incidence of benign and malignant primary cardiac tumors. Primary sarcomas of the heart are rare indeed. Mahaim[3] in 1945 reported 329 primary cardiac tumors of which 87 were sarcomas. This is a proportion of 1:3.7, primary benign tumors being over three times more common than primary sarcomas. Eleven more have been reported, making the total ninety-eight.[1,2,4,8–13,24,26] Our case of primary hemangio-endothelial sarcoma is the ninety-ninth primary sarcoma but only the fourth hemangioreticuloendothelial sarcoma.

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"Sarcomas of the heart may occur at any age, having been found anywhere from the age of 3 to 79 years, most of them coming between 18 and 58 years. They predominate in males, in the proportion of 25 to 16. The apparent duration of the tumor is from one month to 3½ years."[15]

TABLE I
PRIMARY CARDIAC SARCOMAS

Histopathologic Types	No. of Cases
Spindle-cell sarcoma[3,13]	18
Round cell sarcoma[3]	18
Polymorphous cell sarcoma[3]	11
Fibrosarcoma[2,3,10,26]	11
Rhabdomyosarcoma[3,4,8,9]	10
Myxosarcoma[1,3]	6
Unclassified sarcoma[3,11]	6
Giant cell sarcoma[3]	5
Leiomyosarcoma[3,12]	5
Angiosarcoma[3]	3
Lymphosarcoma[3]	2
Fibromyxosarcoma[3,24]	2
Melanosarcoma[3]	1
	98

Clinical Characteristics. Myocardial invasion of a diffusely spreading tumor may be manifested by acute congestive failure, by any of the arrhythmias or by only a very few vague symptoms. With encroachment upon the coronary arteries myocardial anoxia will occur. Doane and Pressman[14] in 1942 reviewed twenty cases of cardiac malignancy, both primary and secondary, which had been diagnosed before death, and then added their own case. Those authors emphasized, as suggested by Yater,[15] that the signs and symptoms fall into two groups. The first class is that in which the symptoms are minimal, vague and suggest little the nature of the lesion. A patient with no clearly definable clinical picture and without symptoms of cardiac dysfunction until terminally, is prone to develop sudden uncontrollable congestive heart failure with unexpected death commonly occurring; or the patient may have symptoms suggestive of subacute bacterial endocarditis. In the second group the signs and symptoms are more definite. Arrhythmias including heart block occur; acute congestive failure without apparent cause, often in a patient with a carcinoma anywhere, a hemorrhagic pericardial effusion especially if it contains tumor cells, fixation of any border of the heart in the fluoroscope, all are signs which should suggest a cardiac neoplasm as well as should bizarre electrocardiographic changes.

Mahaim[3] reported twenty-three cases with a positive ante mortem diagnosis of cardiac neoplasm and five more in which the diagnosis was suggested. In twenty cases the tumor was secondary and in eight it was primary. Hsiung[16] added two more.

CASE REPORT

A twenty-six year old white male veteran entered the hospital on March 2, 1948, in severe congestive heart failure, predominantly left sided. He was extremely dyspneic and irrational so the initial history was obtained from his mother. She stated that the patient first complained of chest pain while overseas in 1943. No further record was available concerning this complaint and apparently the patient got around adequately until January 29, 1948. At that time he experienced pain across the entire anterior chest and at both scapular angles. He had marked dyspnea, profound weakness and poor appetite.

He was treated at a nearby hospital for congestive heart failure and a secondary diagnosis of subacute bacterial endocarditis was made. Sulfonamide therapy followed by penicillin and ultimately streptomycin was employed with no apparent benefits although the patient's condition seemingly improved following a short course of the last-mentioned drug. His illness continued for four weeks and he was then sent home for a brief period before being admitted to Madigan General Hospital on March 2, 1948.

On entry here the patient was seen to be a tall, gaunt, white adult male, with marked pallor and obvious dyspnea. His lips, tongue and skin generally were extremely dry and his temperature was 105.2°F. A marked stomatitis was present. Mentally he was disoriented but passively cooperative.

The heart was regular in force, rate and rhythm with a sinus tachycardia of 120/min. There was gross enlargement of the heart so that the apical impulse was felt in the sixth interspace between the left anterior and mid-axillary lines. P_2 was a grade 4 murmur, coarse and blowing, and markedly accentuated over A_2.

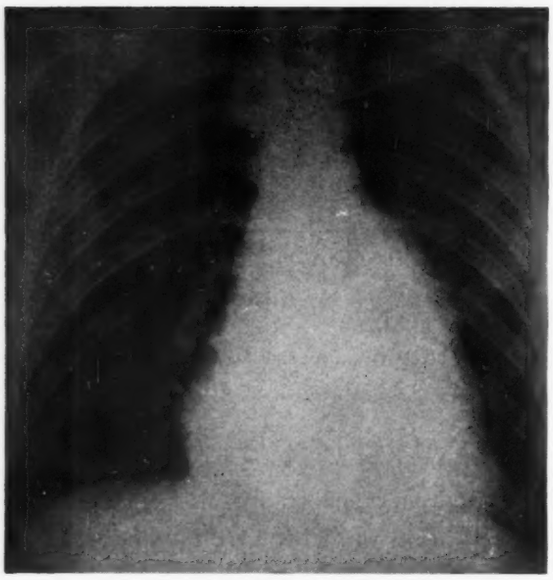

FIG. 1. Postero-anterior film of the chest in our case of hemangio-endothelial sarcoma of the heart. Note particularly the fullness of the pulmonary artery region and the wavy left cardiac margin.

Peculiarly, the other valvular areas were normal. Arterial blood pressure readings averaged 110/70 mm. Hg (R) supine. The lungs revealed coarse rales in both bases posteriorly, especially the left.

For this acute episode he was treated with a regimen based on oxygen, morphine, digitoxin and mercuhydrin to which he responded satisfactorily. Five consecutive blood cultures were obtained following which penicillin was administered in a dosage of 300,000 units every three hours intramuscularly. A satisfactory response was obtained within twenty-four hours but the penicillin was continued for one month. None of the blood cultures became positive. Blood pressure readings ranged between 104/70 to 90/60 mm. Hg between March 24th and April 8th, the latter readings obtaining from April 3rd onward. The apical pulse continued at a rate of 130/min.

Improvement was progressive to a point at which the patient became moderately ambulatory until April 5th. On that date at ten o'clock he became very weak, complained of thirst and exhibited a violet hue over the upper half of the thorax anteriorly. His face remained pallid, with no cyanosis. The liver was enlarged, extending down six to eight fingerbreadths and filling the entire epigastrium. The patient did not complain of pain. He suffered with hypertension and increased venous pressure. Mercurial diuresis was effective in relieving some of the liver congestion. On April 6th he had an unalleviated acute failure of the right heart, unresponsive to protracted energetic treatment, and died quietly on April 8, 1948.

Pertinent positive laboratory data were as follows: prothrombin time: control sixteen seconds, patient twenty seconds. The urine was entirely normal. Blood findings: white blood cells varied from 13,250 on admission to 20,150 just before death. The differential varied as follows: polymorphonuclears from 70 to 86 per cent, lymphocytes from 12 to 24 per cent and monocytes from 2 to 4 per cent. The erythrocytes showed poikilocytosis, polychromatophilia and occasional reticulation; one platelet count was 454,920; hemoglobin was 11.1 gm. on March 17th and 9.3 gm. on March 19th. The sedimentation rate (Wintrobe method) varied from 42 to 53 mm. per hour. The hematocrit varied from 37 to 44. Six blood cultures were negative; the blood Kahn test was negative. The vital capacity on admission was 1,200 cc., 13 per cent of normal, on an average of three tests. Blood chemistry: non-protein nitrogen and the icterus index were normal. Blood chlorides were 514 mg. per cent two days before death. Bromthymol turbidity was normal on two occasions. Serum alkaline phosphatase was 5.9 units.

Bone marrow showed the following: myeloblasts 1, myelocytes 13, metamyelocytes 16, band cells 26, polymorphonuclears 16, lymphocytes 14, normoblasts 14 and red:white ratio 1:6.

X-ray examination showed a "mitral configuration with marked prominence in the region of the pulmonary arteries and conus." (Fig. 1.) Generalized cardiac enlargement was evident. The electrocardiographic findings are presented in Figure 2.

At autopsy the following essential gross findings were seen: The lips were blue. A few petechiae were seen over the left anterior chest and the lower sternal region. There was no clubbing of the fingers. The fingernail beds were cyanotic and contained no splinter hemorrhages. In the peritoneal cavity there were 600 cc. of amber, blood-tinged fluid. The left pleural cavity contained 1,000 cc. of bloody fluid and the right about 600 cc. The left lung weighed 560 gm., the right 840 gm. The tracheobronchial lymph nodes were normal. The pleural surfaces of both lungs were covered with many round, slightly umbilicated, reddish-purple

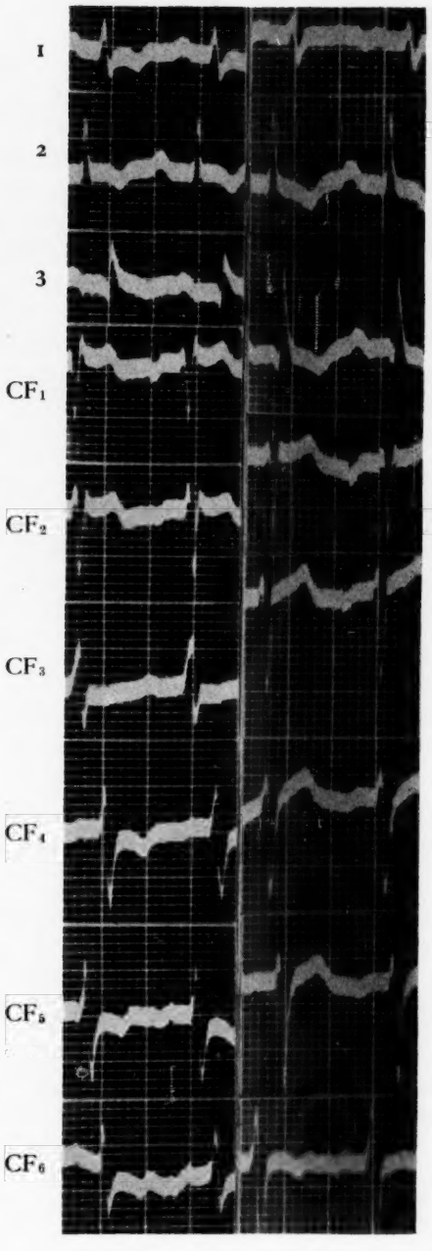

FIG. 2. A, electrocardiographic tracing obtained March 2, 1948. A sinus tachycardia of 116/minute was present, together with right axis strain. Other non-specific changes proved to be inconstant in a series of six electrocardiograms obtained between the above date and April 4, 1948 (four days prior to death). B, tracing obtained March 8, 1948, illustrating the other extreme of the variable pattern obtained throughout the course of the illness. Interim tracings vacillated between the configurations of A and B illustrated here, probably representing mainly right ventricular strain.

hemorrhagic nodules 0.5 to 3.5 cm. in diameter. All lobes were firm and non-crepitant. Marked congestion was evident and the bronchi exuded

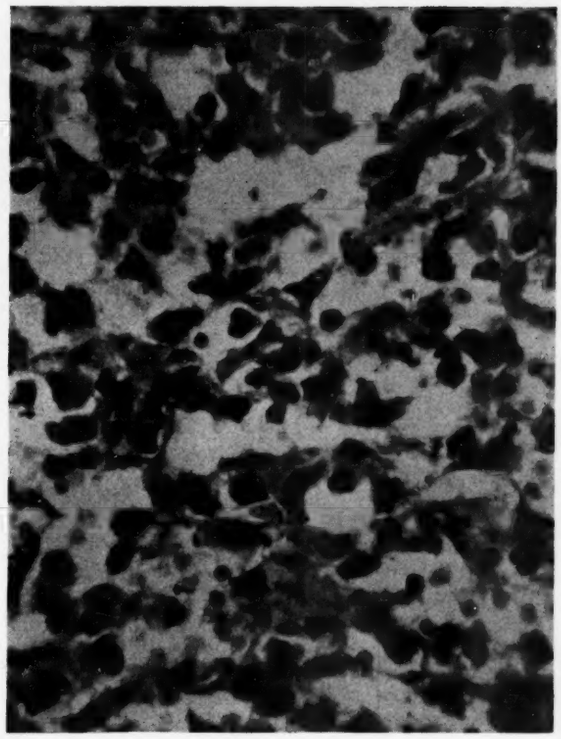

FIG. 3. Showing the vascular spaces comprising the tumor. Their resemblance to young capillaries is noted. Erythrocytes are found in some of them; high power magnification.

hemorrhagic mucus. The pericardium was fibrotic and densely adherent to the epicardium, completely obliterating the pericardial sac and averaging 3 mm. in thickness. The diaphragmatic pericardium was studded with many purple tumor nodules averaging 2.5 cm. in diameter. The heart measured 17 cm. transversely, 22 cm. vertically and 11 cm. in the A-P diameter. With the pericardium it weighed 2,030 gm. The coronary arteries were small and pliable with marked narrowing of their lumen, with no obstruction noted. The myocardium was firm, dark purple-red and bloody throughout. There were many diffuse confluent tumor nodules, some centrally necrotic, in all areas but more on the right side and in the upper 1.5 cm. of the interventricular septum. Large areas of the endocardium of the right ventricle and atrium and about the tricuspid valve were invaded by the tumor. (Fig. 3.) The purple, hemorrhagic neoplastic nodules had amalgamated the heart and pericardium so that the myocardium was 2.5 cm. thick on the right and 3 cm. thick on the left side, the outer 2 cm. of which was muscle. The wall of the apex of the right ventricle was 5.5 cm. thick and the wall of

the pulmonary conus was 4.5 cm. thick. The distance from the base of the tricuspid valve to the right apex was 7.5 cm. and from the base of the mitral valve to the left apex was 8.5 cm. The chorda tendineae and papillary muscles were hypertrophied and bloody on section. Subendocardial hemorrhages were scattered throughout. The valve circumferences were tricuspid 9 cm., pulmonary 9 cm., mitral 10 cm. and aortic 9 cm. All the tumor nodules were strikingly hemorrhagic and blood had infiltrated into all the cardiac tissues. The aorta was normal throughout as were the major aortic and pulmonary branches. The abdominal viscera were congested. The prostate contained a 1.5 by 1.5 by 1 cm. purple-yellow necrotic area in the right lobe.

Microscopic findings were as follows: Sections of the lungs showed marked congestion with many macrophages containing brown pigment. Many sharply defined areas were completely filled with erythrocytes which obscured the alveolar outlines. Some evidence of emphysema was present. A few small nests of tumor cells were found lying loosely without any pattern in the parenchyma. These cells were irregular with scant eosinophilic cytoplasm and irregular hyperchromatic nuclei. Sections of the heart stained with hematoxylin and eosin showed many varying-sized spaces forming what appeared to be poorly formed vascular channels (Fig. 3.) In many places these spaces resembled young capillary tubes. These channels were lined by a loose network of immature cells resembling endothelium in many places. The cells varied in size and shape, had a small amount of pale eosinophilic cytoplasm and hyperchromatic irregular nuclei which had a fine granular network supporting 1–3 central or eccentric nucleoli. The nuclei filled a large proportion of the cell. Some of the nuclear granules were coarse and heavily stained. Some of the cells had phagocytized erythrocytes. Many of these cells were closely grouped forming thin strands connecting larger ones. Between these strands were the vascular spaces previously mentioned. Erythrocytes had engorged many vascular spaces forming solid areas of hemorrhage, some of which were centrally necrotic. The phosphotungstic acid-hematoxylin stain showed a normal amount of reticulum which was not intimately related to the individual cells. No striated muscle cells were found in the tumor areas which had completely replaced the myocardium. The section taken from the left ventricular wall at the junction of the tumor tissue and the myocardium showed the myocardial fibers to be in various stages of degeneration, with infiltration of individual tumor cells. Here the tumor was sharply delineated from the myocardium. There were a few isolated atrophic groups of muscle fibers present in the tumor area. Away from the tumor process the remainder of the myocardium was normal. The coronaries were normal. The liver showed a chronic passive congestion with marked central degeneration and the prostate showed an old infarction.

COMMENTS

No pathognomonic symptoms or signs appear with cardiac tumors. Often the diagnosis is one of exclusion and frequently it is only the peculiarly atypical course of a "cardiac" patient which will suggest this rare possibility. Yater[15] has discussed the topic of symptomatology at length and divides the cardiac tumor patient into those clinical types not suggestive of tumor of the heart and those which are. His classification, however, extends to cover secondary neoplasms of the heart as well as primary tumors of the pericardium.

In our case the diagnosis might have been made on the grounds that (1) no valvular lesion was found clinically which could fit acceptably into any of the well recognized types, congenital or acquired; (2) the atypical clinical course, with unexplained decompensation periods; (3) the progressively altering electrocardiographic pattern and (4) the bizarre postero-anterior chest film. Coupled with these, of course, were the facts that the blood cultures were negative and that the antibiotic agents, penicillin and streptomycin, prescribed at another institution previously had failed to affect the clinical course either of the temperature or of any of the symptoms. Peculiarly enough no conduction disturbances were noted electrocardiographically. Cyanosis, however, had been observed to be distributed oddly over the upper anterior half of the thorax but was unaccompanied by erratically situated edema or unique pulsatile findings.

Weir and Jones[17] in 1941 reported a case with an ante mortem diagnosis of cardiac neoplasm in which their diagnosis was angio-reticulo-endothelioma. In our case the first impression one had from the heart grossly is that it was of vascular origin. Our first impression before opening the heart was diffuse leukemic infiltration or a vascular sarcoma. Figure 4 shows the areas described as dark purple-red in the myocardium proper. These dark areas indeed looked very much like hemorrhage within the myocardium. The diffuse "hemorrhage" or apparent vascular elements grossly involving the entire right and left atrial and right ventricular wall and approximately one-half of the left ventricular walls could not be explained other than by a very diffuse, malignant vascular lesion, most likely sarcomatous.

Of the eighty-seven primary sarcomas of the heart reported by Mahaim[3] the atria were involved in sixty-one; in forty-one of these it was the right atrium. Forty-two of the total had metastasized to the lungs. This last fact is obvious when one realizes that primary cardiac sarcomas are most common on the right side, the metastasis usually being due to endocardial involvement with small tumor particles passing into the lungs from the right ventricle. Primary tumors, the majority of which is benign, are most common in the atria while metastatic tumors are more common on the right side of the heart.

Primary cardiac sarcomas have been reported as polypoid and non-polypoid by Mahaim; or they may be classified as nodular or diffuse. Our case was definitely a diffuse lesion replacing the entire left and right atrial wall, the right ventricular wall and one-half of the left ventricular wall. The tumor possibly originated in the right atrium or ventricle because of the greater diffuse involvement here. The wall of the right ventricle was much thicker proportionately than the left ventricular wall, their normal 1:3 ratio obviously being disturbed. The atrial walls were about equally involved except for the pulmonary conus whose wall was extremely thick.

FIG. 4. Shows the massive and diffuse thickening of the myocardium of the right ventricle and the region of the pulmonary conus.

In a survey of the literature on primary cardiac sarcomas one finds that in many cases the dimensions and weights of the heart and even of some of the tumors were not mentioned. The heaviest heart recorded was in the case reported by Friedman et al.[13] in 1945. The patient, a thirty-four year old male, was followed for several weeks with the clinical diagnosis of a massive ventricular aneurysm following a myocardial infarction. The heart and lungs together were estimated to weigh 2,960 gm. and the heart was estimated to weigh 2,510 gm. In our case the heart weighed 2,030 gm. By far the greater majority of cardiac tumors, whether they are primary or secondary, benign or malignant, has weighed far less than that of Friedman's case or of our own. Yater states that the size of primary sarcomas may vary from the size of a walnut to that of a child's head. He cited a case of a large angiosarcoma which originated in the pericardium and contained a cavity which communicated with the right ventricle. The weight of the heart was not given. He also reported three lymphangio-endothe-

liomas obtained from the older literature, two of which caused complete heart block. One of these was thought to originate in the bundle of His while the other was in the region of the atrioventricular node. He mentioned a hemangio-endothelioma which produced no clinical findings in the patient. These tumors were small enough to be measured in millimeters. Hewer and Kemp[18] in 1936 reported a malignant hemangio-endothelioma of the heart with multiple metastases, and Choisser and Ramsey[19] reported a cardiac angioreticulo-endothelioma (Kaposi's disease) without skin lesions in 1939. It measured 6 cm. in diameter.

Our gross diagnosis was confirmed by finding many poorly formed vascular channels and large collections of very closely packed erythrocytes. The neoplastic cells appeared to be of endothelial origin and replaced over 90 per cent of the entire myocardium showing that this tumor was indeed a diffusely growing one. These findings led us to the opinion that this was a primary cardiac hemangio-endothelial sarcoma most likely originating in the right side of the heart. This neoplasm, we believe, became diffuse by extension along the vessels and lymph channels of the myocardium. (It is well known that the myocardium is very richly supplied with blood vessels which communicate freely with one another.) As the sarcomatous growth extended along the myocardium, it replaced the muscle cells. The extensive involvement makes one wonder how the heart could continue its work as long as it did. The friable endocardial lesions of the right atrium and ventricle were due to extension along the venae minimae and they easily explain the multiple infarctions and metastatic lesions in the periphery of the lungs.

The brain and the testicles unfortunately were not examined, the autopsy being done under trying circumstances. Theoretically it is possible that the lesion originated in the testicles but clinically they were entirely normal. Although a minute focus of neoplastic tissue in the testicles could possibly have spread to the heart without any other metastases, it is highly improbable and extremely unlikely especially to produce this vascular sarcoma. The pelvis was entirely normal as were the abdominal and retroperitoneal and thoracic lymph nodes which were examined meticulously. No tumor involvement was found other than in the heart and lungs.

SUMMARY

This case of primary cardiac sarcoma brings the total recorded to ninety-nine; it is the fourth malignant hemangio-endothelioma of the heart reported. This cardiac sarcoma was found in a twenty-six year old male veteran who exhibited bizarre, unalleviable cardiac symptoms.

This is the 349th primary cardiac neoplasm recorded in the literature through December, 1948.

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Amyloidosis in Hodgkin's Disease*

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THE association of amyloidosis and Hodgkin's disease, although known for a long time, has rarely been reported in American or English literature. As far back as 1856 Wilkes[1] reported a case in which the gross autopsy material strongly suggested the existence of both diseases. Most standard American medical texts and most papers on Hodgkin's disease today, however, either make no mention of the association or casually refer to it in passing. On the other hand, Sternberg[2] and Meyer[3] believe that amyloidosis is not an infrequent complication of Hodgkin's disease.

A review of the literature reveals only twenty-nine cases of Hodgkin's disease in which the concurrent existence of amyloidosis is either demonstrated by pathologic material obtained at autopsy or suggested by clinical studies. These cases have been listed in Table I and the significant findings relative to the amyloid disease briefly described and commented upon. Sternberg[2] mentions the occurrence of amyloidosis in six cases in his series of fifty-two patients with Hodgkin's disease but supplies no clinical or pathologic details. In addition to the published reports another instance in a series of forty autopsied cases of Hodgkin's disease has come to our attention.[4]

The paucity of published cases warrants the following report in which the diagnosis was made antemortem and confirmed by postmortem examination:

CASE REPORT

E. J., a forty-six year old white male, was admitted to the hospital July 13, 1948, complaining of pain in the back, weakness and weight loss for one year. About six years before admission he complained of a sense of pressure in his chest on exertion. This was relieved by the use of nitroglycerin. Shortly after he noted pain in both scapulae and an enlarged lymph node in the right side of his neck. A biopsy of the node was diagnosed elsewhere as Hodgkin's disease. From 1943 to 1947 he noted at various times occipital and bilateral axillary nodes, chest pain, cough and subscapular discomfort. He was treated with intermittent roentgen therapy with relief of symptoms and disappearance of nodes, receiving a total of 19,600 r.

One year prior to admission he developed severe low back pain for which he received a course of nitrogen mustard which gave him transient relief. Six months later another course of nitrogen mustard was attempted but had to be discontinued because of marked retching. X-ray therapy was again given, the patient receiving an additional 11,000 r, but he continued to complain of increasing pain, general weakness and a progressive weight loss of 40 pounds. His past history was not significant except for symptoms suggesting gallbladder disease two years before the apparent onset of his present illness.

Physical examination revealed a pale, sallow, emaciated white male. A few small shotty nodes were noted in the axillary and inguinal regions. An impaired percussion note and diminished breath sounds and vocal fremitus were noted at the base of the right lung. The abdomen was moderately distended and showed the presence of a fluid wave. The liver and spleen were not palpable. There was 3 plus pitting edema of both lower extremities extending to the knees. Blood pressure was 108/78. The other physical findings were within normal limits.

Urine analysis consistently revealed the presence of marked albuminuria with occasional red and white blood cells and infrequent granular casts. A Fishberg test showed a maximum concentration of 1.024. Examination of

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TABLE I

SUMMARY OF REPORTED CASES OF AMYLOIDOSIS IN HODGKIN'S DISEASE, WITH FINDINGS PERTINENT TO THE DIAGNOSIS OF AMYLOIDOSIS

Author	Clinical Findings	Laboratory Findings	Postmortem Findings
1. Wilks[1]	Hepatosplenomegaly, ascites, edema	.....	Amyloid in liver, spleen
2. Pantopidden[5]	.....	.....	Amyloid in intestine
	.....	.....	Amyloid in intestine
3. Buchanan[6]	Splenomegaly, edema, ascites	Urine: albuminuria	Amyloid in liver, spleen, kidneys, intestine
4. Westphal[7]	.....	.....	Amyloid in liver, spleen, kidneys
5. Sternberg[8]	Splenomegaly	.....	Amyloid in spleen
6. Labbé and Jacobson[9]	Hepatosplenomegaly	.....	Amyloid in liver, spleen, lymph nodes
7. Zuppinger[10]	Hepatosplenomegaly	Urine: albuminuria	Amyloid in liver and spleen
8. Warnecke[11]	.....	.....	Amyloid in liver, spleen, kidneys
9. Bloch[12]	Hepatosplenomegaly	Urine: albuminuria	Amyloid in liver, spleen, kidneys, intestines
10. Hess[13]	Hepatosplenomegaly, ascites	Urine: trace of albumin	Amyloid in liver, spleen, kidneys
11. Steiger[14]	Hepatosplenomegaly	Urine: trace of albumin	Amyloid in liver, kidneys, intestine
	.....	.....	Amyloid in liver, spleen, kidneys
12. Meyer[3]	Hepatosplenomegaly, edema	Urine: albuminuria	Amyloid in liver, spleen, kidneys, intestines, nodes
13. Schugt[15]	Splenomegaly	Urine: no albumin	Amyloid in liver, spleen, kidneys
14. Stahr and Synwoldt[16]	.....	Urine: albuminuria	Amyloid in spleen; no mention of presence or absence elsewhere
15. Schalong[17]	Edema	Urine: albuminuria	Amyloid in liver, spleen, kidneys, intestine
16. Crouzon, Bertrand, Lemaire[18]	.....	.....	Amyloid in liver
17. Gsell[19]	Ascites, edema	.....	Amyloid in the center of miliary Hodgkin's granulomas
18. Bannick and Barker[20]	Hepatomegaly	Urine: albuminuria Total protein: 3.8 gm. %; albumin: "27%" Congo red: 75%	Amyloid in liver, spleen, kidneys, adrenals, colon, ileum
19. Powazka and Mankowska[21]	(listed in Index Medicus)		
20. Udaondo and Segura[22]	Hepatosplenomegaly, ascites, hydrothorax	.....	Amyloid in liver, spleen, kidneys, lymph nodes
21. Cetingil[23]	(listed in Index Medicus)		
22. Tobias and Colombi[24]	Hepatosplenomegaly and anasarca	Urine: albuminuria Total protein: 4.33 gm. %; albumin: 2.09 gm. % Congo red: 100%	Amyloid in liver, spleen, kidneys, adrenals
23. Lehman[25]	Hepatosplenomegaly, edema	Urine: albuminuria Total protein: 4 gm. % Congo red: 65%, 100%, 67%	Amyloid in liver, spleen, adrenals, lymph nodes
24. Cervera and Podesta[26]	Hepatosplenomegaly, anasarca	Urine: albuminuria Total protein: 5.94 gm. % albumin: 1.54 gm. %	Amyloid in liver, spleen, kidneys
	Hepatosplenomegaly, edema and ascites	Urine: albuminuria Total protein: 5.49 gm. % albumin: 3.13 gm. % Congo red: positive	No autopsy*
	Hepatosplenomegaly, ascites	Urine: trace of albumin Congo red: positive	No autopsy*
25. Jackson and Parker[29]	Splenomegaly	.....	Amyloid in liver, spleen, kidneys, lymph nodes

* Hodgkin's disease diagnosed by biopsy; amyloidosis by positive Congo red test.

the blood revealed moderate to severe anemia of the hypochromic type. The white blood cells were not remarkable except for a moderate polymorphonuclear leukocytosis. Total serum proteins were 4.8 gm. per cent, of which 2.8 gm. per cent were albumin and 2.0 gm. per cent globulin. Later studies revealed a drop of the total proteins to 4.3 gm. per cent of which 2.2 gm. per cent were albumin. Blood calcium was normal. The serum alkaline phosphatase was 21.8 King-Armstrong units. Blood urea nitrogen was normal. Phenolsulfonphthalein excretion and urea clearance tests showed significant diminution of renal function. The Congo red test showed 76 per cent absorption from the blood in one hour. Sternal marrow studies were normal. Serial x-rays of the chest revealed a progressively increasing infiltration in the right mid-lung field and a bilateral pleural effusion. A large destructive area in the left iliac bone and an increased density of the second lumbar vertebra were noted in an x-ray survey of the skeleton.

During the patient's hospital stay his pain progressively increased and failed to respond to any treatment, including intravenous procaine and a course of teropterin. Supportive measures were of no avail. Additional roentgen therapy was considered inadvisable. The toxic symptoms previously noted discouraged the further use of nitrogen mustard. Progressively increasing doses of narcotics were required to control his pain. The edema noted on admission increased until marked anasarca of the face, legs, arms and body resulted. The hydrothorax and ascites also increased. Slight response was obtained by the use of mercurial diuretics. The course was progressively downhill and the patient died on September 24, 1948.

Postmortem examination revealed the following: The body was that of a poorly developed, malnourished middle-aged white male. There was generalized anasarca but no palpable lymph nodes.

Each pleural cavity contained 1,500 cc. of a grayish, turbid fluid in which fibrin clots were floating. There were no adhesions. The right lung weighed 400 gm. and was atelectatic. There was a firm nodular area approximately 4.5 by 2 cm. in diameter in the lower part of the right upper lobe which on section revealed a mottled gray and white granular surface. There was one small cavity within this mass which contained necrotic material. The small bronchi leading to this mass were not unusual. No other nodules were found. The left lung was normal.

In the mediastinum there was a mass of fibrous tissue approximately 8 cm. in diameter intimately bound to the ascending aorta and the roots of the vessels arising from the arch. This mass did not compress the vessels. On section it was homogeneously white and firm. Small areas of calcification were scattered throughout its substance. The heart was normal.

The abdominal cavity contained 3,000 cc. of slightly turbid, grayish fluid. There was a mass of fibrous nodular tissue in the region of the porta hepatis which did not encroach upon any of the structures in this area. On section its surface was similar to that of the mediastinal mass. A few isolated fibrotic lymph nodes were found along the superior border of the pancreas. On section these also were similar to the mediastinal mass.

The liver weighed 2,000 gm. The capsule was smooth and shiny and the edges were slightly rounded. It was firm and on section showed a waxy brown appearance. The gallbladder and extrahepatic ducts were normal.

The spleen weighed 170 gm. The capsule was slightly wrinkled and the cut surface appeared waxy. Tiny, soft, round, gray nodular areas were scattered throughout its substance giving it a "sago" appearance. No other lymph nodes or masses were found in the abdominal cavity.

The right kidney weighed 165 gm. and the left 200 gm. The capsules stripped with ease and revealed a fatty yellow-streaked, finely granular surface. On section the characteristic renal architecture was exaggerated. The cortices and many of the medullary rays were bright yellow. The cortices varied from 6 to 9 mm. in thickness. The pelves were not unusual. The adrenal glands were not enlarged but were firmer than normal. On cut section the surface appeared waxy.

Microscopically the architecture of the masses found in the left lung, mediastinal and portal regions was almost obliterated by fibrous tissue. In the few remaining cellular areas the tissue consisted of a loose stroma with various-shaped small mononuclear cells. There was an abundance of lymphocytes, many eosinophiles, occasional large mononuclear cells and a rare giant cell of the Reed-Sternberg type. (Fig. 1.) Many of the cells could not be identified. There were no focal areas of necrosis. There was no

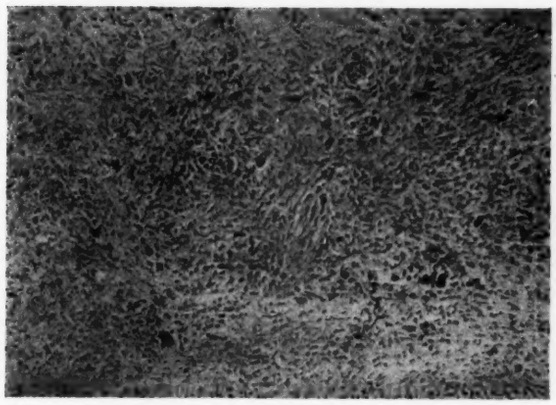

FIG. 1. Lung tissue is replaced by a compact fibrous stroma which contains a pleomorphic cellular infiltrate; note the multilobed nucleated giant cells; hematoxylin and eosin stain, × 60.

FIG. 2. The liver cord cells are compressed by amyloid deposition in the sinusoids; hematoxylin and eosin stain, × 60.

evidence of Hodgkin's disease in the spleen or in any of the other organs.

Amyloid was found in the spleen, liver, kidneys and adrenal glands. In the spleen it was focal in distribution obliterating the Malpighian corpuscles. There was abundant amyloid in the liver causing marked compression of the liver-cord cells and slight thickening of the walls of the portal vein and arteries. (Fig. 2.) In the adrenal gland the amyloid was found mostly in the zone fasciicularis and reticulosum. In the kidneys the amyloid caused marked alteration in almost all of the glomeruli and afferent arterioles. (Fig. 3.) There was an excess of intracellular fat in the tubules and polaroscopic examination failed to reveal cholesterol bodies. There was no amyloid found in any of the other organs examined.

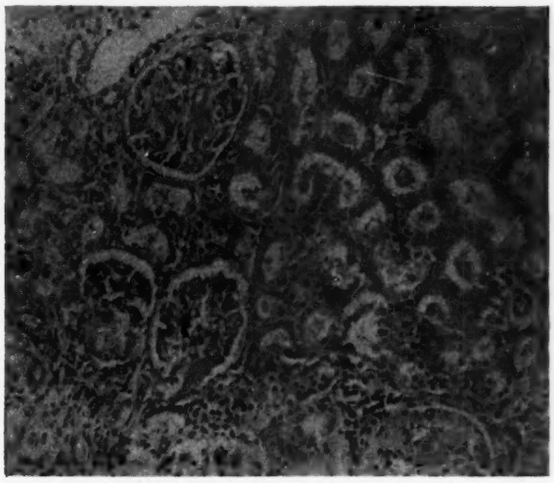

FIG. 3. In the kidney the glomerular architecture is altered by amyloid; there is protein material in the tubular lumina; hematoxylin and eosin stain, × 60.

COMMENT

From analysis of the tabulated data the co-existence of Hodgkin's disease and amyloidosis appears to be more than a coincidence. Sternberg[2] found six such cases in his series of fifty-two patients with Hodgkin's disease. In addition, all the reported cases are typical of the secondary type of amyloidosis, that is, involvement chiefly of the liver, spleen, kidneys and adrenals. This is in contradistinction to primary amyloidosis which usually involves the heart, lungs, skin, mucous membranes and tongue.[27] Although a small percentage of the primary cases may show a "secondary" type of distribution, the fact that all the available reported cases fall into this latter category would tend to rule out a casual association of Hodgkin's disease and primary amyloidosis.

There seems to be no association between amyloidosis and any specific form of Hodgkin's disease. The reported cases fall into all categories and have the same sex and age distribution as Hodgkin's disease in general.

Hepatosplenomegaly cannot be used in determining the presence or absence of amyloid disease with any certainty. Although amyloidosis is frequently characterized by hepatosplenomegaly, Uddstromer[28] has shown in his series of uncomplicated Hodgkin's disease that 63 per cent had

splenomegaly and 36 per cent hepatomegaly. Of the twenty reported cases of amyloidosis in Hodgkin's disease with available clinical information 80 per cent had splenomegaly and 65 per cent hepatomegaly.

Edema, ascites and pleural effusion can all be produced by the compression of various blood vessels and lymphatic channels by Hodgkin's tissue as well as by the hypoproteinemia secondary to the albuminuria of renal amyloidosis. Consequently the presence of edema, ascites or hydrothorax cannot be used as differential criteria.

Uncomplicated Hodgkin's disease even with involvement of the kidneys has not been reported as producing albuminuria. In eleven of fifteen cases of associated amyloidosis and Hodgkin's disease with adequate study, marked albuminuria was noted. In three of the remaining four at least a trace of albumin in the urine was found. One can presume that proteinuria occurring during the course of Hodgkin's disease points to a complicating factor. Amyloidosis must be carefully searched for as a possible cause of the urinary findings.

Congo red tests were made in five of the reported cases, and in our own case. All of these could be interpreted as positive if one accepts a 60 to 100 per cent absorption of Congo red from the blood as diagnostic of amyloid disease. From these data one can conclude that the presence of proteinuria and significant absorption of Congo red from the blood are the most reliable criteria for determining the presence of amyloid in Hodgkin's disease.

In the case presented in this report the outstanding clinical features at the time of our observation of the patient were due to the presence of amyloid disease. At postmortem Hodgkin's disease was found to be extremely limited in extent and could not be considered to involve any vital structures. The marked ascites, generalized anasarca and pleural effusion were not due to Hodgkin's disease *per se* but followed the marked loss of protein in the urine. The profound weakness and possibly the premortem shock syndrome may have been enhanced by the amyloid involvement of the adrenal gland.

SUMMARY*

1. Thirty-five cases of co-existent amyloidosis and Hodgkin's disease were collected from the literature. Of these twenty-nine have been summarized and tabulated.

2. An additional case is reported together with the criteria for diagnosis.

3. Amyloid disease is a complication of Hodgkin's disease. When excessive amounts of protein appear in the urine or progressive anasarca of a generalized nature develops, amyloidosis should be carefully looked for.

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* Since the submission of the above report, Short and Castleman (*New England J. Med.*, 241: 497, 1949) have described another case of Hodgkin's disease, with secondary amyloidosis involving liver, adrenals, kidneys and lymph nodes. These authors also report that in sixty cases of Hodgkin's disease at Massachusetts General Hospital five had amyloidosis. In addition, Dahlin (*Ann. Int. Med.*, 31: 105, 1949) in a survey of the Mayo Clinic experience with secondary amyloid disease reported two cases of thirty due to Hodgkin's disease. One of these has probably already been cited above.[30]

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Book Review

Malignant Disease and Its Treatment by Radium. By Sir Stanford Cade. 2nd ed., vol. 1, 383 pages. Baltimore, 1948. The Williams & Wilkins Company. *Price* $12.50.

The first edition of this book appeared in 1940 as a single volume of 1,280 pages. The present edition is to be published as four separate smaller volumes. The first volume is subdivided into two parts, "The Radioactivity of Radium" and "Biological Effects of Radiation." The material is of rather broader interest than the titles of the book or its part might indicate. The stated object is first, an account of malignant disease, second, to indicate the choice of treatment and only third, to detail the methods of radium therapy. Throughout much of this volume one might read "radiotherapy" for "radium" for it is repeatedly emphasized that x-rays and radium produce a similar response in tissue.

The chapter on general considerations offers a healthy orientation concerning the choice of treatment in malignant disease. The author believes that success here lies in coordinated teamwork and not so much in the method as in its efficient application.

There is an excellent survey of the duration of untreated cancer. This should be the measure of the value of any method of treatment, but information on this aspect of the disease is not common knowledge. The life expectancy of a patient with untreated carcinoma of the breast is 3.25 years, a figure which should temper satisfaction with early good results in treated patients.

The chapters dealing with physics and dosimetry cover fundamental aspects with adequate references for sources of specific and detailed information. The section on interstitial therapy, radium plaques and teletherapy are by C. W. Wilson, L. H. Gray and H. T. Flint. Information on dosage to radium workers by stray radiation and on protection is included.

Under a discussion of the effects of radiation on normal tissues the description of skin reaction is worthy of close attention. The stages of skin reaction are clearly described with serial histologic illustrations. A knowledge of the essential changes in skin in patients receiving intensive radiation therapy would be helpful to the clinician concerned with the possibility of radium or x-ray burn. The section dealing with the hematopoietic tissues offers detailed information on patients and radium workers, applicable to radiation effect from any source. This is a concise account useful to any who may anticipate a need to care for patients exposed to radioactive materials.

The chapter "Tissue Culture and Experimental Radiology" is a new addition to the book. In the hands of the pathologist tissue culture has become an important aid in establishing the diagnosis in undifferentiated tumors. Apart from its wide application in clarifying the biologic action of radiation, the method may also be useful in determining the prognosis in a given case while the patient is still under treatment.

The last chapter "Dangers of Radium and Protection" is perhaps the most valuable section of the volume. Here the author presents twenty detailed case histories of radium burn. This represents a part of experience that is not proportionately reported in the literature. Radionecrosis is not necessarily an ill result for in some instances it has been the price of a favorable outcome in an otherwise incurable disease. The course of this complication may be prolonged and difficult of management and it would be of great benefit if more information of this nature were available.

Although this extensive review of experimental and clinical observation is documented with 575 references, occasional information of some importance lacks notation of source or basis. The sterilization dose for the human ovary is given as 280 r for x-rays generated at 180 kv. (p. 231) and as 840 r for radium (p. 336). These values are not necessarily conflicting but some amplification concerning the time factor and technic would be necessary for practical application.

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1. Rosenblum, H. and Fraser, L. E.: Proc. Soc. Exper. Biol. and Med., 65: 178, 1947.
2. Dry, T. L., et al.: Proc. Staff Meetings Mayo Clin., 21: 497, 1946.
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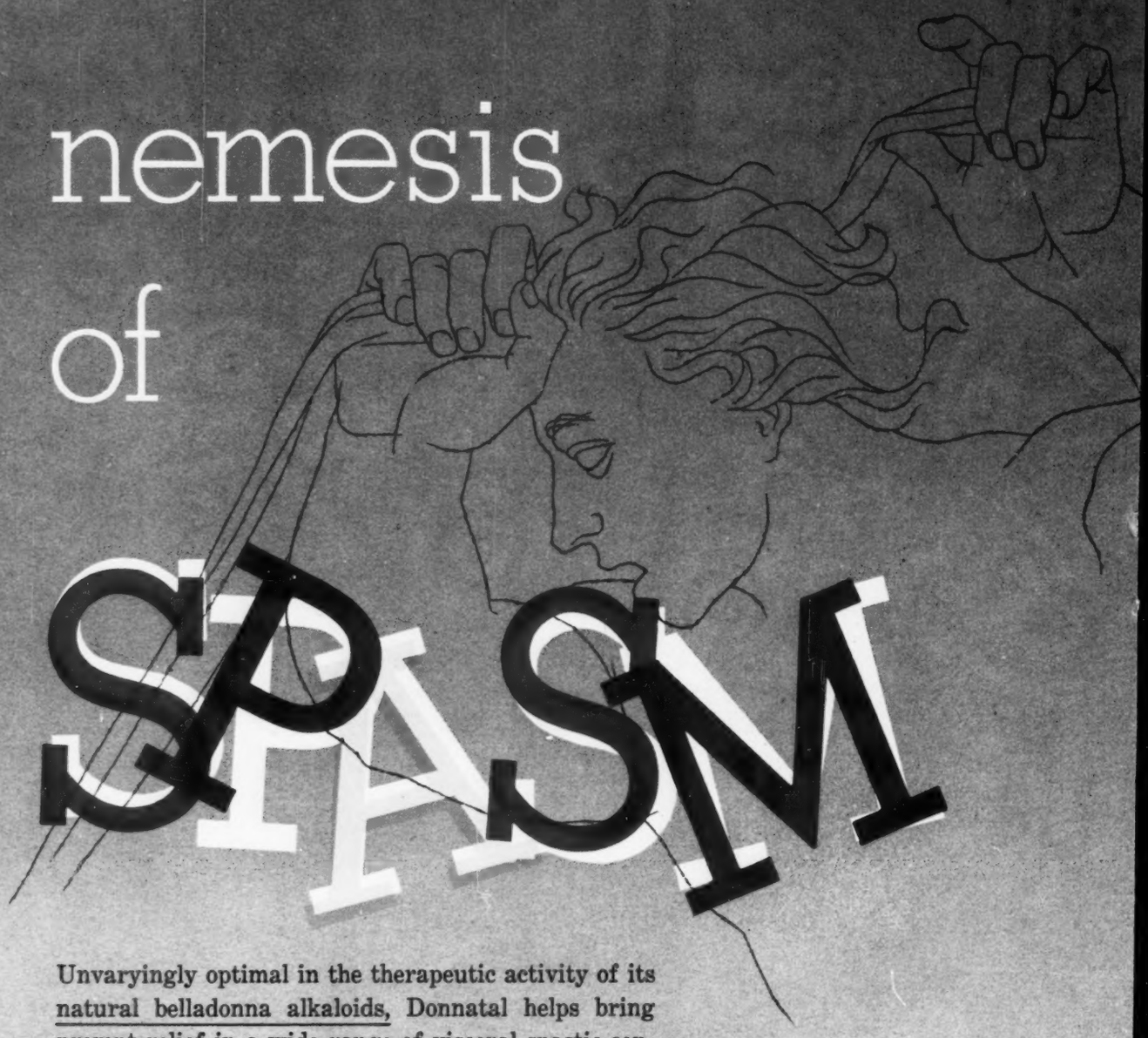

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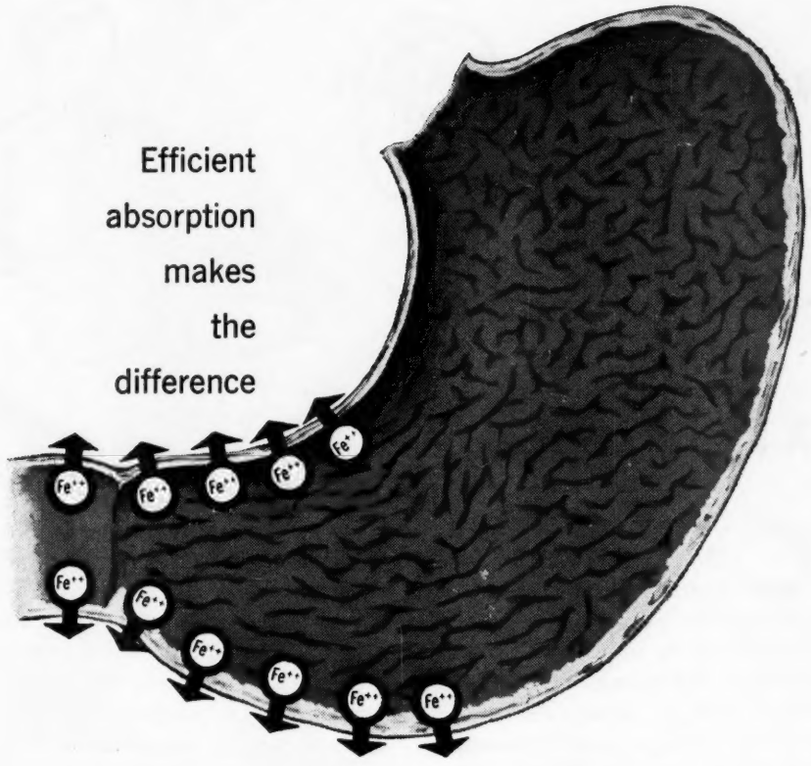

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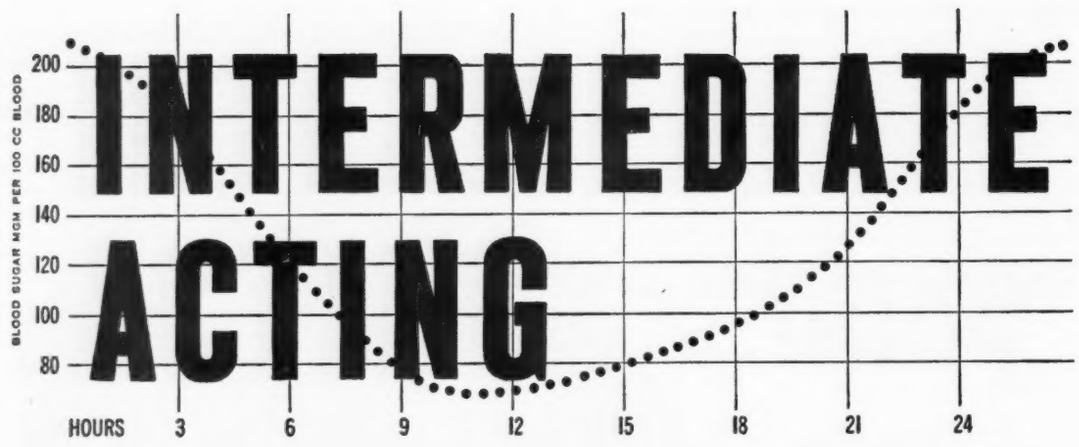

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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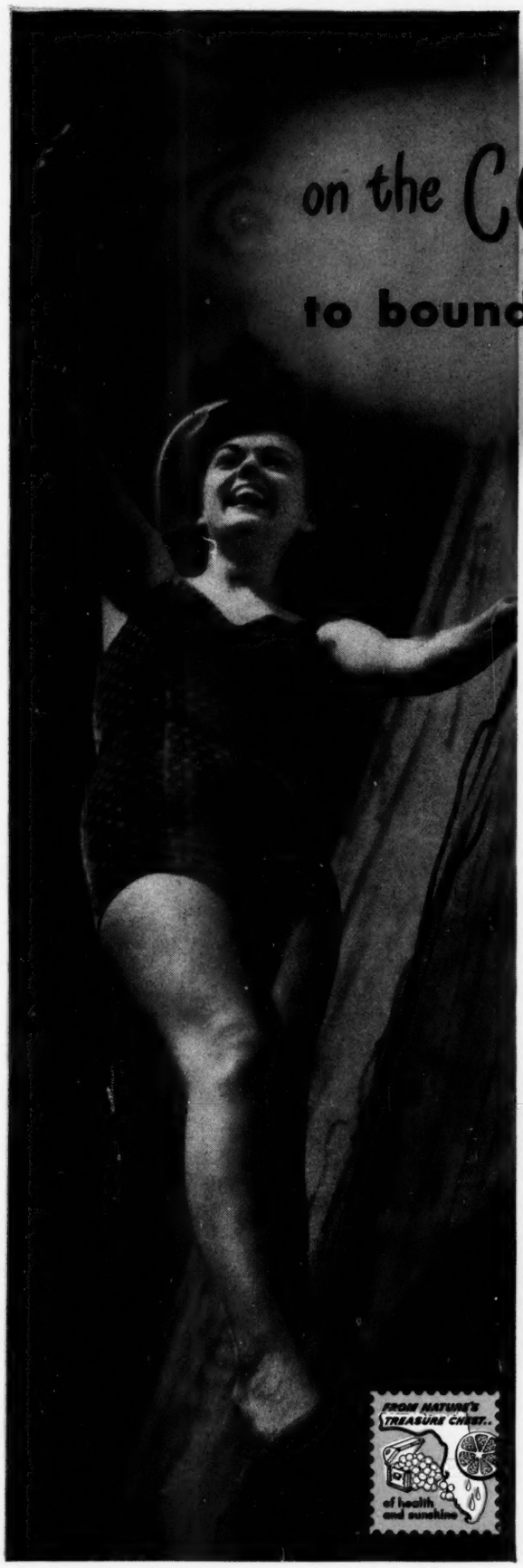

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References: 1. Gordon, E.S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947. 2. Manchester, T.C.: Food Research, 7:394, 1942. 3. McLester, J.S.: Nutrition and Diet, Saunders, 4th ed., 1944. 4. Rose, M.S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944. 5. Sherman, H.C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946.

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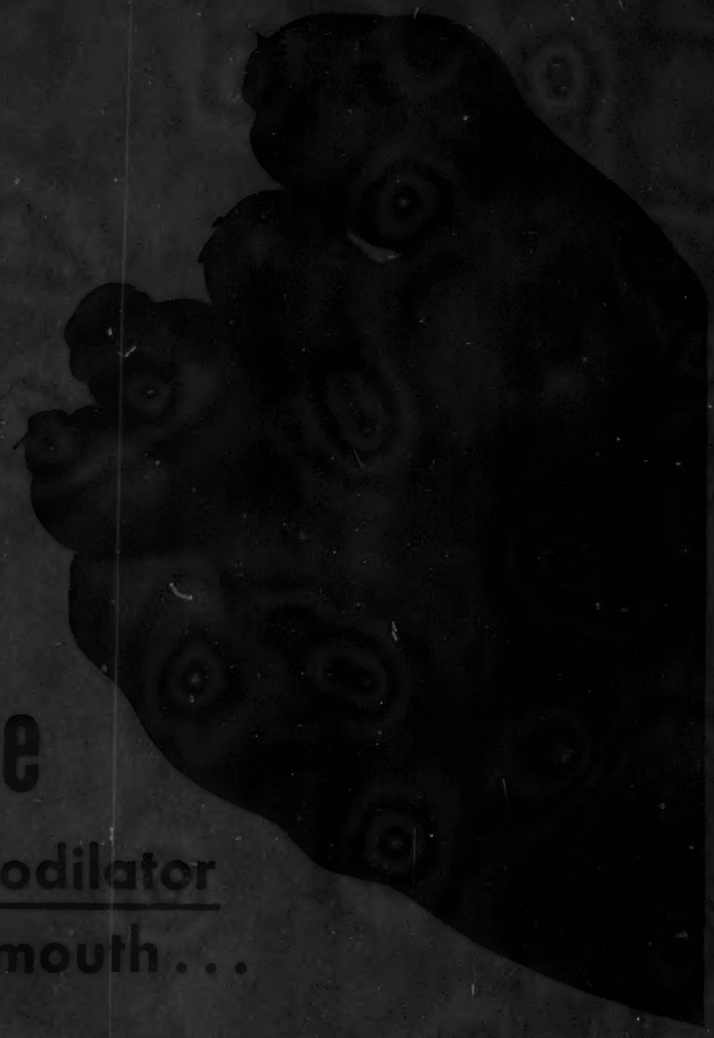

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1. Rogers, Max P.: J.A.M.A., May 21, 1949.
2. Wyatt, Bernard L.: Ann. West. Med. & Surg., Aug. 1949.
3. Gebauer, Marquis, Saunders & Hendrix: Ann. Surg., 127:5, May 1948.

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